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## OBSERVATIONS ON THE CYSTS OF *INTAMOLBA* *TETRAGENIA*\*

S F DARLING, M D  
ANCON, C Z

When we consider the medical history of Panama with reference to the origin of its population the negroes from Africa and possibly the Pacific Islands, Chinese, introduced by the French Canal Company, Coolies, Sikhs and Bengalis from India, besides those representatives of the Caucasian race who have come from every portion of the tropical and subtropical world, Americans from the Philippines, various globe-trotters and 'tropical tramps,' we naturally expect to encounter here some of the diseases especially characteristic of other lands, and we are not surprised to find that echinococcus infections are confined strictly to Spanish laborers. Infection by *Taenia nana* and *T. saginata* occurs among Europeans and Americans. Bilharziosis comes almost exclusively from the French West India Islands, *Polaria demarquai* in negroes from St Vincent, Old World hookworms, *A. duodenale*, among the West Indians, possibly introduced there by coolies. Trichinosis has been detected only among the Spanish (from Spain).

Some of these diseases are absolutely confined to the races or nationalities mentioned, because the local environment here is quite unsuited for their transmission to the native population. For example, there is no instance of any kind of tapeworm or fluke infection among the native population. It is otherwise, however, with hookworm disease. For the Old World worm is now found in many of the West Indians and in some Panamanians.

If a sailor infected with aestivo-autumnal malaria from the west coast of Africa should have a sufficient number of gametes in his peripheral blood on arriving here, and be bitten by *Anopheles albimanus*, 60 per cent of the mosquitoes would become infected and might later transmit the disease to others, the secondary cases would clinically conform to the local type of malaria, and there would be no difference in morphology between the plasmodia and those in cases seen here.

\* Manuscript submitted for publication in THE ARCHIVES Sept 25, 1912

If we compare too, the pathological features of those native diseases which are also found elsewhere in the tropical world, we find that they are practically identical. Oriental sore, black-water fever, yellow fever, leprosy and malaria present the same features wherever encountered.

To the practiced eye of the pathologist there is something specific about the appearances of the lesions caused by the pneumococcus, tubercle bacillus and meningococcus, when, for example, the meninges are involved, and a histological examination of tissue confirms the opinion based on the gross appearances. It is usually possible by a mere inspection of a temperature chart to distinguish from each other cases of relapsing fever caused by *Sp. recurrentis*, *Sp. duttoni* and *Sp. novyi*. If these premises are true, then if there be more than one variety of pathogenic entamebic infection it may be presumed that the cosmopolitan population of Panama would sooner or later disclose some evidence of the different types. For the disease requires no specific transmitting agent, but infection follows in the same way as typhoid fever or bacillary dysentery. We should expect to find at least the two alleged types described elsewhere, and we should expect to find some sufficiently well-marked differences in the lesions caused by the two species of entamebas. Such is not the case, however. In my autopsies at Ancon Hospital during the past seven years, the entamebic lesions have presented a characteristic, unique and unvarying pathology, and these lesions have the same character as those described from the Philippines and other tropical countries, if we are to judge from the descriptions and illustrations in the literature on the subject, and the opinions of medical men with a Philippine experience who have seen the cases here.

If we consider some of the protozoal diseases infecting man and animals, we may note that their sexual or perpetuating forms offer no difficulty of detection. Gametes of malaria may be found in almost every untreated case of malaria when carefully looked for. In coccidiosis of animals the oocysts are always in evidence in the stools. Cysts of *Lambia intestinalis*, *Trichomonas vaginalis* and other intestinal parasitic flagellates are easily detected in the stools in cases of infection by their respective flagellated forms. Cysts of *Entamoeba coli* may be found in every case of infection by this entameba, and cysts of *Entamoeba tetragena* may also be found when specially looked for, in untreated cases not fatal, in imperfectly treated cases and in chronic cases, as well as in some cases before a relapse.

Is it not strange that the reproductive cycle of *E. histolytica* showing the formation of spores by budding has been so rarely seen? Schaudinn<sup>1</sup> described it from a case of dysentery contracted in China, and Craig<sup>2</sup> has

1 Schaudinn Arb a d k Gsndhtsamte, 1903, xix, 547

2 Craig Am Med, Phila., 1905, ix, 854, 897, 937

confirmed Schaudinn's findings, while Hartmann,<sup>3</sup> who has examined some of Schaudinn's original preparations of *E. histolytica*, is of the opinion that most of them are *E. tetragena*. Practically all other observers of *E. histolytica* have had to content themselves with descriptions of the trophozoites of the large vegetative forms, or of the smaller forms, and on these they have based their determination of species.

If we make a careful study of the entamebas found in our cases of dysentery and liver abscess using a technic which brings out as well as possible the morphological features in the nucleus of the trophozoites and in the cysts, we can be of no other opinion than that there is but one pathogenic entameba and that one is *E. tetragena*.

We have too long been biased by the posthumous influence of Schaudinn. We have used too carelessly the Romanowsky stain with dry-fixed films for the identification of entamebas. We have been content to base our diagnosis on observations limited to the large trophozoite found in the stools in dysentery and in pathological tissue and to call the trophozoite "*E. histolytica*". We have neglected to follow our cases during and after recovery, and we have failed to observe in neglected cases the forms representing the perpetuating phase of *E. tetragena*, namely, the small generation and the cysts, both of which have been overlooked or have been mistaken for *Entamoeba coli* and monad cysts.

We should give attention to the work of Hartmann, who, with his pupils, has established the fact that the common pathogenic entameba of all tropical and subtropical lands is *E. tetragena*.

While collecting and studying specimens of entamebas from clinical cases and autopsy material in Panama, I have had very little difficulty in observing nearly the complete developmental cycle of *E. tetragena*, but an insurmountable difficulty has been encountered in attempting to discover the first trace, in any of the entamebas seen here, of a developmental phase such as that described by Schaudinn and Craig, and I am forced to the conclusion that *E. histolytica* is not present in Panama, and influenced by the researches of Hartmann and Whitmore, by Walker's recent work in Manila, in connection with my own observations on tetragena cysts in the moist-chamber, and by animal experiments, I am inclined to doubt whether it has ever existed anywhere.

Great as Schaudinn undoubtedly was as a protozoologist gifted with a wonderfully penetrating mind in the observation of the life histories of protozoa, skilled in the difficulties of technic and possessing a scientific imagination of wonderful power in interpreting phenomena in his field, there is a steadily growing opinion that he made a number of errors. Novy has advanced reasons for believing that

3 Hartmann Lehrbuch d. Protozoenkunde (Piowazek), Barth, 1911



Schaudinn was mistaken with regard to the life history of *Trypanosoma noctua*, and Hartmann as mentioned above believes that he was misled by degeneration forms in describing *E histolytica*.

Schaudinn studied the peculiar forms from which he described *E histolytica* in but one single case of entamebic dysentery, and his interpretations have been accepted and applied to many cases elsewhere by several observers. If *E histolytica* be the common entameba of tropical lands as we have hitherto supposed, it is extraordinary that so little testimony has been adduced in evidence that this entameba has existed in any other person than Schaudinn's Chinese case. It is true that Craig has confirmed Schaudinn's work in connection with the development of entamebas by spores. But Craig's illustrations indicate that some at least of the forms drawn by him as *E histolytica* were *E tetragena* and that his technic was not calculated to bring out such distinctions as are necessary for the purpose. In studying the spore formation of *E histolytica*, Craig seems to have relied on dried<sup>4</sup> films stained by a modification of the Romanowsky stain. If one collects from the literature the illustrations of "*E histolytica*" and of *E tetragena* and compares them it will be seen at once that the writers have been calling *E histolytica* the large trophozoites seen in dysenteric stools, these frequently display no karyosome but they can be demonstrated as *E tetragena* by animal inoculation or by the history of the case. On the other hand the illustrations of *E tetragena* show that the writers have been dealing with the reduced forms or small generation which are the lineal descendants of the large trophozoites. Elmassian indeed, a trained protozoologist, working with the reduced form of *E tetragena*, described it as "*E minuta*," a distinct species.

The importance of Craig's work is in insisting on the truth that there are two parasitic entamebas for man, *E coli* and a pathogenic form and we owe to him a considerable debt of gratitude for this work, for he was for years the chief if not the sole influence in America opposed to the sincerely advocated but pernicious views of the culturalists, or those who believed (in fact some still believe) that the pathogenic entameba may be cultivated on protozoal agar.

The subject is of more than academic importance, for now that Hartmann has established the wide-spread distribution of *E tetragena* and all our cases of dysentery here are caused by the same entameba, we should begin at once the investigation of some of the important questions vital to this disease, such as the viability of *E tetragena* cysts in the outside world, the conditions in the host which lead to the pro-

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<sup>4</sup> In a strain of *E tetragena* from kittens I found artefacts in certain films that had been dry-fixed and stained by Romanowsky. These might easily have been described as the budding forms and spore formation of *E histolytica*.

duction of cysts, the influence of medication on cyst production; the susceptibility of domestic animals to infection and their agency as carriers, and the number and kind of cysts necessary to infect. It is this aspect of the question that is of greatest importance.

It would seem that infection in man occurs through the mouth by the ingestion of cysts. In two recent cases a cook and a child in the family who harbored cysts appeared to be the carriers. The individual with acute symptoms of dysentery is not usually infectious, for he is merely harboring the large vegetative form which, to judge from the results of animal experiments, is digested and cannot serve to infect. It is the unsuspected individual who has recovered from an attack and who may have formed stools or possibly diarrhea, whose stools contain cysts that is the carrier of infection. The importance, therefore, of examining stools of recovered patients and in fact all clinical cases as well as of persons in contact with clinical cases of dysentery, for the detection of carriers, is very great. I have detected cysts in several individuals in whom they were unsuspected. The commonest location for entamebic lesions in our cases here has been the cecum. Cases of this type may give no evidence of infection other than colicky pains in that region, but they are undoubtedly fertile carriers of cysts. The stools of cyst-carriers are usually solid and contain no dysenteric elements—one of the reasons why tetragena cysts have been so long overlooked or misinterpreted.

The cysts are round, refractive bodies about 15 microns in diameter. They have no doubt been mistaken for monad cysts but may be differentiated from them by the fact that the latter vary a good deal in size, are either smaller or larger and have crescentic margins. The cysts may be seen in fresh preparations to have one, two or four nuclei, some have refractile blocks of chromidia. When the cysts are quite homogeneous in the fresh stool, they will after exposure to the moist chamber or in vaselined films become differentiated in a day or two so that one, two, or four nuclei may be seen. In some preparations after several days in the moist chamber it is possible to note that the cysts contents are ameboid, and rarely, if one is fortunate, the emergence of amebulae may be noted. When it is desired to stain them, films should be made, wet-fixed and stained with hematoxylin.

The mode of treatment appears to have a very important relation to cyst production. I have observed cysts in several chronic and untreated cases and in a patient treated by means of rectal injections which probably did not reach the lesions higher up; but I have detected cysts in only one case in twenty-eight that had been treated by means of very large doses of bismuth subnitrate. In these cases the stools contained from 9 to 10 per cent by weight of bismuth subnitrate. It

would appear that when most cases of entamebic dysentery are treated energetically by this medicament, the vegetative or large pathogenic generation is at once removed, leaving none to propagate the small generation from which the cysts arise

Cases treated energetically by oral medicaments may fail to disclose cysts, for the vegetative entamebas do not have time to develop a resistant small generation with cysts. This is analogous to the destruction of all malarial merozoites by means of large doses of quinin at the beginning of an attack and thus killing all the potential gametes

The investigations of Hartmann,<sup>5</sup> Viereck,<sup>6</sup> Werner<sup>7</sup> and Whitmore<sup>8</sup> have shown the wide-spread distribution of *E tetragena* as a cause of entamebic dysentery. The paucity of evidence which we possess on the subject of the perpetuating forms of *E histolytica*, and the likelihood of *E tetragena* being the chief, if not the sole, cause of entamebic dysentery in man, leads me to report these observations, for I am unaware of any published records of observations on the fate of *E tetragena* in the outside world. Material from three cases has been studied

#### CASE REPORTS

CASE 1—Hospital No 105,730. This case was the first one positively identified here as an infection by *E tetragena*. The patient was admitted Sept 5, 1911. It was his first time in the hospital. His complaints were referable to an infection by malarial plasmodia which were found in his blood. He stated that his bowels were regular. He remained in the hospital fourteen days, received 3 grains of calomel and three doses of magnesium sulphate. The total number of stools for the period was 51, an average of 3.6 daily. On one occasion it was noted that pus was found in the stool, this was on September 14. On September 8 many small entamebas (Fig 10) were detected in the stool and these I identified as *E tetragena*. The patient was discharged September 19, and returned to work. In this case there is no history of dysentery. Evidently the lesion in the colon was high up, most probably in the cecum.

The stool of November 13 contained trophozoites, schizonts and cysts and in stained specimens four nucleated cysts were detected.

Through the kindness of Drs Connor and Weinberg I obtained specimens of the man's stool after he had returned to work. The stools were solid but contained many small tetragena cysts. All of those observed were homogeneous, for nuclei and chromidial blocks could not be detected in the fresh specimen. Cultures on protozoal agar and tap water broth were entirely negative for trophozoites, and cysts disappeared completely from the stools and cultures within seven days.

On November 13 vaselined coverslip preparations were made with the fresh stool. The cyst contents appeared perfectly homogeneous, nuclei and chromidial blocks were not seen. November 14 the interior of the cysts had become coarsely

5 Hartmann Handbuch d Path Protozoen (Prowazek), Barth, Leipzig, 1911, Installment 1

6 Viereck Studien über die in den Tropen ewarhene Dysenterie, Beihefts z Arch f Schiffis- u Tropenhygien, 1907, No 11

7 Werner Studien über pathogene Amoben Beihefte z Arch f Tropen- und Schiffshygiene, 1908, xii, part II

8 Whitmore Arch f Protistenkunde, 1911, xxiii 1, Centralbl f Bakteriöl, Orig, 1911, lviu 234

granular. November 15 many of the cysts were seen to have four nuclei imbedded in finely granular protoplasm. November 18 there was a space between the cyst capsule and the granular central mass. The latter had become mulberry-like in form and was seen to slowly move on itself in an ameboid fashion. The nuclei within the mass were from time to time plainly discernible, disappearing as they rose or fell from the optical plane during the ameboid motion (Fig 14). Some of the cysts were filled out completely by the granular mass. Some had two nuclei others had four, while some had no nuclear figures at all. The protoplasm was always granular. A motile bacillus was seen in the subcapsular space in several specimens. The capsule of some became invisible as though of the same refractive index as the surrounding medium. A number of the cysts had disappeared at this time for the number was very definitely reduced.

CASE 2—Sr. A. April 9 1912. The patient was an adult male living in the city of Panama. He was suffering from an attack of entamebic dysentery and his stools contained much bloody mucus and many entamebas. With gentian violet by the *intra vitam* method the submembranous granules of the nucleus of the entamebas stained distinctly and some individuals had a faintly staining centriole and others appeared to have a faintly staining karyosome. Rectal injections of the infected stool eight hours old into very small kittens were negative. Hematoxylin stained preparations showed the trophozoite to be of the large vegetative type in which the karyosome was only seen in certain individuals and did not stain at all deeply. Dry fixed preparations stained by Hastings and Giemsa's stains showed the nucleus as containing a fine red oxychromatin reticulum not usually arranged in the form of a ring.

The patient was placed on treatment by his physician in Panama. This consisted of astringent rectal injections. He has reported to me from time to time on each occasion bringing a specimen of his stool. On May 20 he returned from the interior appearing to be in much better physical shape and free from dysentery. A specimen of stool just passed was free from dysenteric elements but contained many one two and four nucleated tetragena cysts all containing blocks of chromidia (Figs 7 11 and 12).

On June 13 the patient returned with a specimen of hard formed stool. He stated that he had had no return of dysentery, but was continuing the rectal injections. The stool contained many tetragena cysts, and portions were placed in a moist chamber and in sterile tap water, to note developmental changes. June 27 no cysts could be detected in the patient's stool, which was a solid one. July 17 a good many tetragena cysts were found in specimens of a formed stool passed this morning all contained nuclei and chromidia.

Summary of Findings. April 9 the stool contained pus, blood, mucus, and many large trophozoites, only a few of the latter revealed a karyosome when stained by gentian-violet and iron-hematoxylin. In other words, most of the trophozoites would be described as "*E. histolytica*." Rectal injections of the stool eight hours old into two very small kittens failed to infect.

May 20, the stool was formed and contained no vegetative trophozoites, but many one-, two-, and four-nucleated cysts of *E. tetragena*. In moist-chamber preparations, all the cysts disappeared within five days. Feeding experiments on very small kittens with cysts from this stool on the day of passing were negative.

June 13 the stool was formed and contained many tetragena cysts but no trophozoites. In moist-chamber preparations the cysts rapidly diminished in numbers so that very few were seen at the end of twenty-four hours. No cysts could be demonstrated at the end of six days in hematoxylin stained preparations and none could be demonstrated in coverslip preparations of the six- and ten-day-old stool. Preparations of the stool which had been put up with sterile tap water for nineteen hours contained some four-nucleated cysts (Fig 13).

About 10 grams of feces that had been in the moist chamber for three days, were taken up with water and milk and passed into the stomach of two half-grown cats, but no infection resulted during a period of eight weeks.

## EXPLANATION OF FIGURES IN PLATE

1 The large trophozoite (Phosphotungstic acid hematoxylin) endoplasm and erythrocytes are shown, the centriole and karyosome and peripheral chromatin are conspicuous

2 Trophozoite with primary division of nucleus into four nuclei This form is rarely seen and is believed to be a schizont, it may become the form seen in Fig 3

3 Four nucleated trophozoite (schizont?)

4 Trophozoite gamete (?) seen in Case 3, May 14, apparently a larger size of 5 and 6

5 Trophozoite gamete (?) of small size seen in Case 3, May 14, probably a larger form of 6

6 Small trophozoite gamete (?) arising from a cyst

7 Trophozoite of small generation becoming encysted, central sac of fluid (?) and blocks of chromidia are shown

Two trophozoites (gametes ?) from Case 3 May 14, a number of couples were seen together in this way, the nuclei were always of different types The ectoplasm was apparently sticky for the organisms could not separate, but moved around and around

9 Trophozoite of small generation becoming encysted, the nucleus is vesicular and the chromidia is seen condensing around the periphery of the fluid sac

10 Trophozoite of the small generation containing chromidia

11 Binucleated cyst containing chromidia One of the nuclei shows division of its centriole

12 Quadri-nucleated cyst

13 Quadri-nucleated cyst unstained, from moist chamber preparation, second day, the cyst contents are homogeneous save for 4 nuclei represented by peripheral refractile granules of chromatin

14 Mulberry mass in a cyst from moist chamber, fifth day, contains four amebulas with granular cytoplasm, nuclei and ameboid outline unstained One nucleus is not displayed as it was not in the optical plane

15 Mononucleated cyst containing two blocks of chromidia, one of the type that stains unusually deeply

16, 17, 18, 19 Mononucleated cysts from moist chamber preparations forty-eight hours old, the last three showing a fluid sac

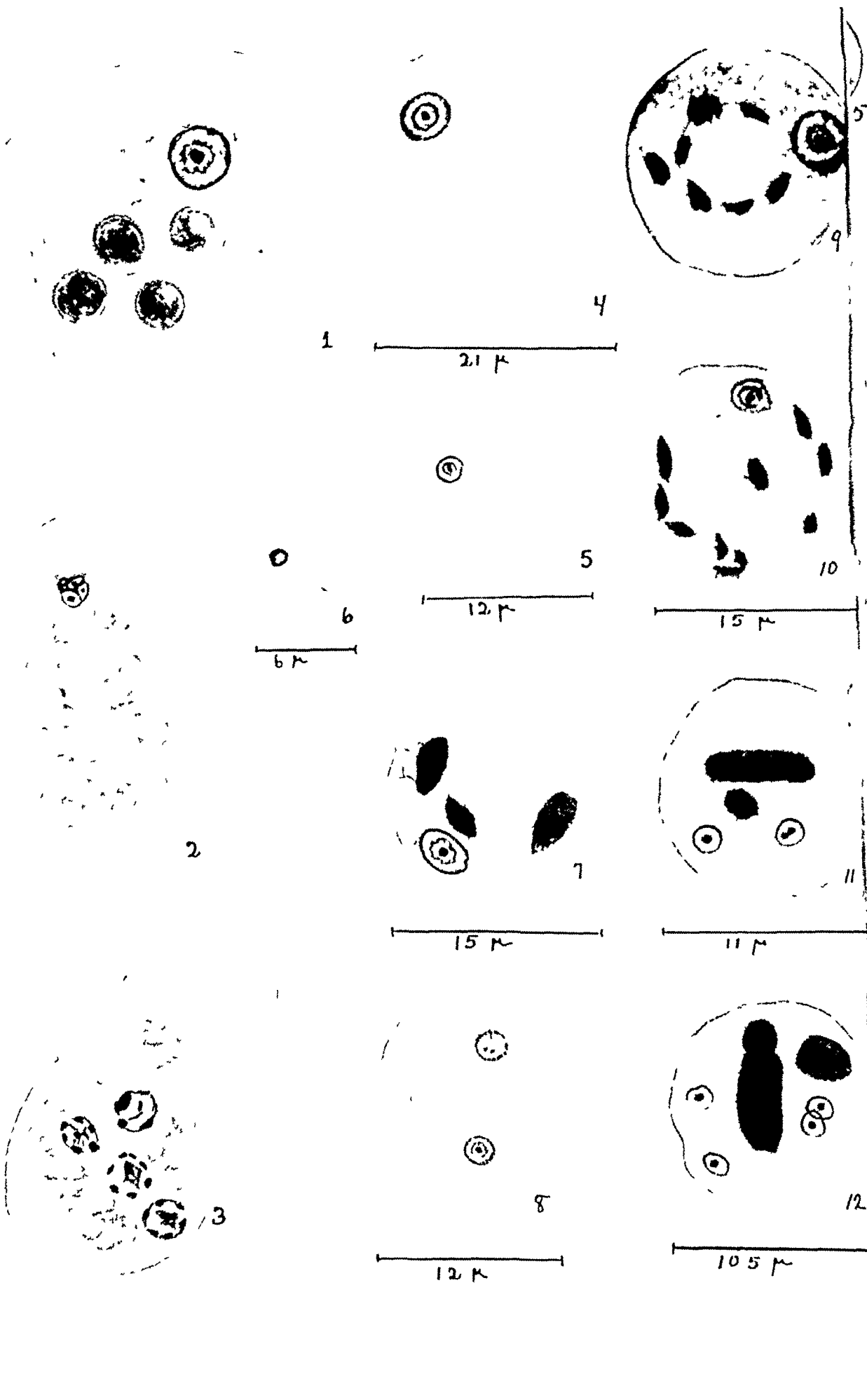
20 23 Binucleated cysts from moist chamber preparations, forty eight hours old

24 Quadri-nucleated cyst

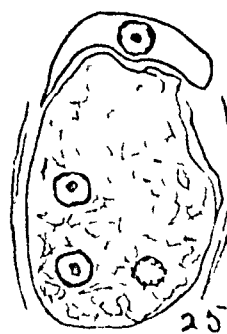
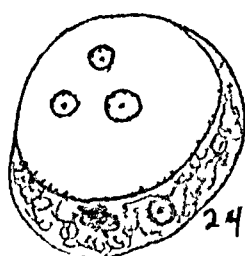
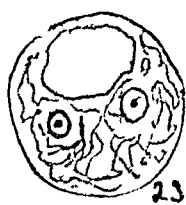
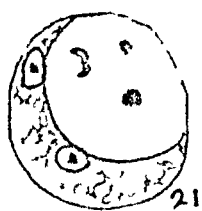
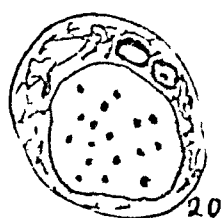
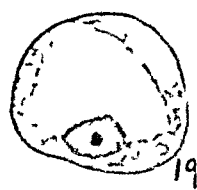
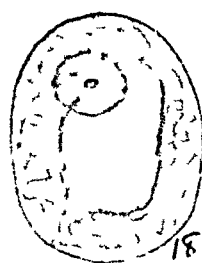
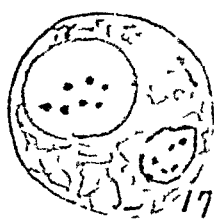
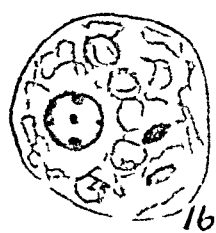
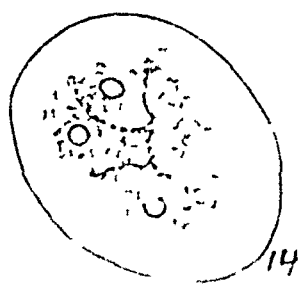
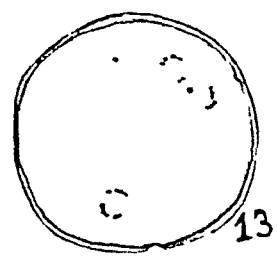
25 Cyst from moist chamber after four days One of the amebulas (gametes ?) has become separated from the rest though it is still enclosed by the capsule of the cyst Two of the nuclei stain well, one apparently has degenerated

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Note—No 3 was stained with iron hematin after fixation with Schaudinn's fluid, No 1 with phosphotungstic acid hematoxylin after Zenker fixation This shows the effect of technic in transfixing and displaying variously the nucleus, particularly the karyosome ring











Smear preparations of the moist chamber specimens contained only one cyst in three films, a considerable reduction of numbers within seventy-four hours.

A quantity of the stool that had been put up for three days with ten volumes of sterile tap water was added to diluted milk and passed into the stomach of two kittens but no infection resulted in a period of over eight weeks.

Six coverslip preparations from the stool that had been in contact with tap water for three days were quite negative for cysts apparently a complete disappearance of cysts when in contact with water for this period of time.

June 27, no cysts nor trophozoites were detected in the stool, which was well formed.

July 17 the formed stool contained a good many cysts (three or four to the high dry field). After twenty-four hours in the moist chamber, there was an appreciably smaller number, and after forty-eight hours, very few cysts could be detected.

In this case, the gradual disappearance of cysts in cultures is seen and the lack of infectiousness of the stool for kittens after three days, probably due to an insufficiency of cysts. This case shows too the persistence of cysts in a patient treated by means of rectal injections which do not reach the upper portion of the large bowel namely, the cecum, where the commonest location of the entamebic process is. The absence of cysts from the stool on one occasion as well as their appearance in solid stools is also noted.

CASE 3—Hospital 111761. I had an opportunity of examining material from this case through the kindness of Drs. James and Carter. The patient had been treated for entamebic dysentery, and on Jan. 11, 1912, a specimen of his stool contained trophozoites and cysts which I identified as *E. tetragena* (Fig. 9). On April 2 the patient had returned to the ward for treatment and his stool on this date contained scybala with bloody mucus containing many large trophozoites such as are usually found in entamebic dysentery (Fig. 1). The trophozoites were about 30 microns in diameter, were finely granular and possessed a rather unusual mode of locomotion. They moved from place to place with a rolling, flowing motion rather more continuous than intermittent.<sup>9</sup> Some had phagocytosed erythrocytes. When stained with hematoxylin, they showed a well defined karyosome, but no cysts nor trophozoites with chromidia were detected. The dysentery disappeared after a few days and on April 11 and 12 a few cysts were seen. A solid stool on April 12 contained a few trophozoites which were very refractile and were stained *intra vitam* by gentian-violet. The stain was taken up slowly but intensively, and revealed a typical *tetragena* nucleus with a well defined karyosome.

On May 14 the patient's stool contained enormous numbers of cysts and small-sized trophozoites. These were placed in moist chambers and examined from day to day after fixation in Schaudinn's fluid and staining with hematoxylin.

*Fresh Stool of May 17*—One is struck at once with the appearance and large numbers of the small trophozoites. Sixty-five per cent are trophozoites and 35 per cent are cysts. These trophozoites (Fig. 4) are about 21 microns in length by 12 microns in breadth. They have conspicuous nuclei, many of them showing rather deeply stained karyosomes and the so called cyclical changes in the centriole. The cytoplasm is vacuolated, the vacuoles being three microns and under in diameter. Many have engulfed bacteria but none had phagocytosed erythrocytes. None of these trophozoites contained chromidia, but they are associated with spherical or slightly ovoid cysts 12 to 15 microns in diameter, which contain one

<sup>9</sup> Trophozoites of *E. tetragena* have two types of motion, an impulsive intermittent one seen in the large, globular, refractile forms, and the flowing continuous motion seen in the elongated non-refractile forms.

or more coarse blocks of chromidia (Fig 7) There is usually a large fluid (?) containing sack or vacuole and a conspicuous nucleus Sometimes there are two or four nuclei It would appear that these cysts have developed from the trophozoites with which they are associated Besides these forms there are some smaller trophozoites ranging in size from about 4 microns up to full size (Figs 5 and 6) Some have nuclei exactly like those of the four nucleated cysts and they are undoubtedly derived from them A few four-nucleated forms, however, are seen which do not appear to be encysted They are usually elongated and not spherical These are undoubtedly four-nucleated schizonts Confirmatory of the opinion that this is their nature, I may say that I have seen a few naked four-nucleated forms (Fig 3) in the pus from an entamebic liver abscess (autopsy 2,760), and these four-nucleated forms were associated with a few small amebulas as well as large trophozoites In the stool of Case 3 on January 11, I observed a trophozoite, the nucleus of which had divided into four small daughter nuclei (Fig 2), these were in apposition and occupied the place and area of that of an ordinary sized nucleus of a trophozoite, it was undoubtedly becoming a four-nucleated schizont Fifty per cent of the cysts are uninucleated 23.5 per cent binucleated, and 26.5 per cent quadrinucleated

*Moist Chamber Preparation After Twenty Hours*—At this time it is evident that many forms have disappeared Apparently there has been a reduction of 50 to 75 per cent in the total number, due chiefly if not entirely to the complete disappearance of the trophozoites The forms now seen are encysted (Figs 15 to 24) and resemble those cysts seen in the fresh stool, although most of the chromidia has now disappeared A few cysts present appearances indicating most positively an ameboid movement within the cyst wall, and the emergence of amebulas It is these small amebulas which are the precursors of the "agamous" trophozoites, concerned in entamebic dysentery For infection follows the feeding of cysts while it invariably fails when only the trophozoites are fed There is still a number of small amebulas (Fig 6) to be seen but no gradation of sizes and no full sized trophozoites (Fig 4) It is evident that the amebulas perish in the fecal mass in moist-chamber preparations This is in contrast with the appearance noticed in the fresh stool for in the favoring environment of the intestinal tract the young amebulas had increased in size

*Moist-Chamber Preparation After Forty-Eight Hours*—There is a still further reduction in the number of cysts, the cytoplasm of which appears to be more homogeneous and usually free from the achromatic sac of fluid (?) noted previously The cysts are round or ovoid Rarely one contains chromidia A few small free amebulas are seen but no full-sized trophozoites

*Moist Chamber Preparation After Three days*—A still further reduction in the number of cysts Four nucleated forms appear to predominate Otherwise, the preparations resemble those of the day before

*Moist Chamber Preparation After Four Days*—The number of cysts appears to be reduced over those in yesterday's preparation It is impossible to estimate this accurately, however, from smears Several cysts to day contain traces of eroded chromidia as though it had been etched off the surface for nutritive purposes A number of cysts are somewhat irregular in contour and represent the ameboid changes noted on previous days, and in cover-slip preparations from Case 1 Some free amebulas are seen (Fig 25)

*Moist-Chamber Preparation After Six Days*—Very few cysts are seen, and considerable time is required to find a sufficient number on which to make observations The irregular contour of the cyst contents is even more exaggerated than in yesterday's preparation

These changes noted in the cysts are analogous to those seen in *E coli*, and differ entirely, of course from those to be seen in free living forms

The cysts require a moist medium for their development Drying interferes with nuclear division and emergence of amebulas from the cysts This is seen from the following experiment About 5 grams of feces from Case 3 on May 14,

containing many cysts and trophozoites of the small generation, were spread over the surface of a porous plate which had been sterilized within a petri dish. The porous plate absorbed moisture from the feces and the resulting film remained as dry as the surrounding atmosphere. After a period of seven weeks the film was moistened with sterile tap water and smears were wet fixed and stained with hematoxylin. The resulting picture was just like that of the fresh stool, excepting for the change due to desiccation. The trophozoites and cysts took the stain very well, particularly the nuclei and chromidia, but they presented a flattened out and warped appearance.

The larger portion of the moistened film was fed to two half-grown cats, but no infection resulted, although this would certainly have provoked entamebic enteritis if the same amount of fresh material had been used.

This is interesting in comparison with Schaudinn's experiment in which he claimed to have induced infection in a cat with dried material containing spores of *E. histolytica* six weeks old.

The developmental changes in the cysts of *E. tetragena* can best be studied in just such a case as the one described, in which there is an enormous number of encysting forms, and these forms appear in some cases in perfect showers.

It would seem that the large 'agamous' trophozoite luxuriates during the acute stage and in active lesions associated with tissue necrosis where nutrition is plentiful. As a result of immunity on the part of the host, or from other causes not as yet known, a reduction in size in the trophozoite occurs. Pearl<sup>10</sup> and Calkins<sup>11</sup> have shown that the 'conjugating generation' of *Paramecium* consists of individuals of measurably smaller size than those of the usual pond water. There is also a difference in the physical and chemical make-up of the cells by which the protoplasm becomes much more sticky, so that two individuals upon meeting frequently fuse at any point." This is referred to because of the fact that the generation immediately preceding the cysts is very much reduced in size and in the fresh stool of Case 3 on May 14, a number of trophozoites were seen as though partly fused together, and possibly represented conjugation. In all cases of infection by *E. tetragena* either in the bowel or liver, a few smaller forms 15 to 24 microns in diameter may be seen, and forms containing chromidia may also be detected when specially looked for. I have seen in a fatal case large trophozoites 30 to 40 microns in diameter, deep in the submucosa, while in the superficial sloughs of the ulcer only small refractile forms were seen. In the fresh preparations nuclei could not be demonstrated in the smaller forms, and when they were treated *intra vitam* with gentian-violet, they took up the stain with extreme slowness compared with the larger more deeply lying trophozoites. These smaller forms are about 15 microns in diameter and contain

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10 Pearl Biometrical Study of Conjugation in *Paramecium* Biometrika 1907, v, No 3

11 Calkins Protozoology, 1909, Lea and Febiger, New York and Philadelphia

no erythrocytes but several blocks of chromidia. This small chromidia-containing generation occupies a stage between the large trophozoites and the cysts.

The appearances in the cysts with regard to fertilization have been interpreted variously. Hartmann<sup>12</sup> and Doflein<sup>13</sup> have figured and described changes which they interpret as autogamy, while Walker<sup>14</sup> sees only a straight forward nuclear division in the cysts. Elmassian,<sup>15</sup> who studied most minutely in a mixed infection of *E. coli* and *E. tetragena*, the small generation and cysts of *E. tetragena* under the name of *E. minuta*, has described appearances which he has interpreted as autogamy. In the very rich collection of cysts furnished by Case 3 on May 14, I have failed to find positive evidences of autogamy such as have been figured by Hartmann and Elmassian, in spite of the fact that I have used phosphotungstic acid hematoxylin, which is probably the most accurate of hematoxylin stains for entamebas fixed with diluted Zenker's and Flemming's solutions.

In the stool of Case 3 on May 14, there is one feature rather difficult to explain. The trophozoites (Fig 4) are 15 to 16 microns in diameter, always devoid of erythrocytes and usually devoid of chromidia, differing thus from pathogenic trophozoites (Fig 1) and the common small-chromidia-containing generation (Fig 10) respectively. The trophozoites contain bacteria, and have evidently been living a vegetative existence in the lumen of the bowel, but although they contain no chromidia they are associated with cysts which nearly always contain several blocks of chromidia (Figs 11 and 12), and they are associated also with small and half grown trophozoites (Figs 5 and 6) exactly like them in staining characters. Is it possible that these trophozoites (Fig 4) have developed in the bowel from cysts and are living a parasitic and non-pathogenic existence in the intestinal lumen, but which would take on an appearance like the pathogenic trophozoite after they had gained entrance to the bowel wall? The very small forms have arisen from cysts or from schizonts, most certainly from the former, for the latter were rarely seen, and these very small forms in turn may develop into the trophozoites just described. If this is true, the precursors of the cysts, which we should expect to contain chromidia, are not present in this specimen. On the other hand, if the cysts develop from the non-chromidia-containing trophozoites, when does the chromidia appear on the scene? for the non-chromidia-containing trophozoites disappear

12 Hartmann (Handbuch d. Path. Protozoen (Prowazek), 1911, Barth, Leipzig) more recently would seem to be of the opinion that *E. tetragena* is analogous to *E. blattarum* and does not exhibit autogamy.

13 Doflein, F. Lehrb. d. Protozoenkunde. Ed. 3, Fischer, Jena, 1911.

14 Walker. Philippine Jour. Sc., 1911, vi, 259.

15 Elmassian. Centralbl. f. Bacteriol. Orig., 1909, li.

completely in twenty hours, at which period there were many chromidia-containing cysts. Unfortunately it is impossible to determine from these preparations whether the trophozoites all perish or whether they develop into cysts. I am inclined to believe that they perish in the moist-chamber, for the number of cysts seen on May 15 was about the number seen on May 14, minus the trophozoites. It will be important in the future to note from hour to hour the changes in the small generation.

The chromidia of the cysts appeared to be used up in the course of nuclear division, for its margins usually became eroded (Fig 21), yet in some four-nucleated cysts uniformly contoured blocks of chromidia were seen (Fig 12).

Counts of the different types of cysts and trophozoites were made from day to day and from different films, and are here tabulated.

COUNTS OF THE DIFFERENT TYPES OF CYSTS AND TROPHOZITES IN A RECENT STOOL MAY 14 (CASE 3)

Trophozoites, 15 microns in diameter containing bacilli but no i b c with prominent karyosome ring, no chromidia 48.3 per cent Cysts 34.9 per cent	Half-grown trophozoites 9.6 per cent	Very small recently emerged trophozoites 5.6 per cent	Four nucleated schizonts 1.6 per cent			
Recent Stool of May 14	Percentage of Different Forms in Moist Chamber Preparations After					
	Recent	20 Hrs	2 Days	3 Days	4 Days	6 Days
One nucleated cysts	50	47	50	31	34	33
Two-nucleated cysts	24	20	18	27	25	33
Four-nucleated cysts	26	33	32	42	41	33
Number of individuals counted	67	*101	*109	*102	*24	*15

\*Very small amebulas were present but could not be counted with any accuracy.

The stool was a pure culture of *E. tetragena*, as were stools in Cases 1 and 2, and the moist-chamber preparations were kept in sterile petri dishes and handled carefully so as to avoid aerial contamination by free-living forms. Fortunately, free-living forms did not develop in any of the preparations, though it is not an uncommon experience for them to appear in cultures of feces. Smears were made and wet-fixed with Schaudinn's bichlorid alcohol and stained with hematoxylin. Good results were obtained with non-alum-hematoxylin and phosphotungstic acid-hematoxylin with a final differentiation by means of potassium permanganate.

Two half-grown cats were fed with material from the stool of May 14 that had been in a moist chamber forty-eight hours. Both animals had prolapse of the rectum at nearly the same hour, twelve days later. The prolapse followed intussusception starting from an inflammatory patch in the lower ileum from which many large trophozoites were obtained. *These trophozoites, although arising from tetragena cysts, presented the nuclear characteristics of E histolytica, E tetragena and E nipponensis.* From this experiment, it can be seen that identification of species cannot be based on appearances noted in the "agamous" trophozoites, and further, it is seen that the alleged differences between *E tetragena* and *E histolytica* and *E nipponensis* are due to unusual physiological or pathological distributions of basichromatin within the nucleus of *E tetragena*.

#### CONCLUSIONS

These cases illustrate the cyst production of *E tetragena*, its intermittency, the absence of cysts during acute symptoms and their presence in formed stools long after the subsidence of acute symptoms.

The gradual disappearance of cysts in moist chamber preparations with a concomitant loss of infectiousness of the stool, and the loss of infectiousness by drying for seven weeks are shown. The development of amebulas within the cysts and their emergence and fate in the fecal mass is described.

It would appear that infection in man is the result of the contamination of food with a small amount of fecal matter containing a great many cysts, during the first day or two after passing.

In one experiment, kittens were fed with a pure culture of tetragena cysts forty-eight hours old. This caused lesions in the small bowel in which large trophozoites were found with the nuclear characters of *E tetragena*, *E histolytica* and *E nipponensis*. This not only favors the opinion held of the identity of *E histolytica* and *E nipponensis* with *E tetragena*, but it shows that specific identification of *histolytica* and *nipponensis* cannot be made from the large vegetative trophozoites alone but the essential features of the life cycle must be seen.

The very great importance of examining the stools of all convalescent and recovered cases of entamebic dysentery for cysts, and thus detecting "carriers" is made apparent, for it is the cyst that is the infecting agent and not the large trophozoite.

# SYPHILITIC AORTITIS ITS DIAGNOSIS AND TREATMENT<sup>1</sup>

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For some years I have been much interested in the condition which is now generally known as syphilitic aortitis or mesoaortitis. At first my observations were particularly directed to the pathological lesion itself, later the exact etiology of these changes became the subject for study, while at present it is the diagnosis and treatment of the disease to which most time is devoted. Up to the present I have had an opportunity at the Pennsylvania<sup>1</sup> and University hospitals in Philadelphia, and at the Presbyterian Hospital in New York of studying sixty-three cases in which syphilitic aortitis was proved to exist at autopsy, or in which the diagnosis seemed reasonably sure from the combination of certain symptoms and signs, with a positive Wassermann reaction during life. Of the entire number, twenty have been treated with salvarsan. But except for the fact that the diagnosis and treatment of this disease are of such importance, and that the observations have perhaps suggested certain lines for further study, it would scarcely be justifiable to offer such a familiar subject for serious consideration.

Since the time of Morgagni, syphilis has been recognized as a factor in the etiology of aneurysm, as well as of other less well defined cardiovascular diseases, but it was not until the publication of the anatomical studies of Dohle,<sup>2</sup> in 1888, followed by the work of Heller and his pupils on syphilitic aortitis that the direct relationship between the two was made apparent. Dohle's excellent description and illustrations of the pathology of syphilitic aortitis really leaves little to be added on that score, while the accounts of the French, and particularly Huchard,<sup>3</sup> Dieulafoy,<sup>4</sup> Gallavardin<sup>5</sup> and Fournier<sup>6</sup> of the symptomatology and diagnosis of "*Aortite sub-aiguë*," a subject to which they have devoted much attention, and to which Germans and Anglo-Saxons until recently have paid comparatively little heed in spite of the original account by Cor-

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<sup>\*</sup>Submitted for publication in the ARCHIVES Oct. 21, 1912.

1 For an opportunity of studying the cases at the Pennsylvania Hospital I am indebted to Drs. Morris J. Lewis, J. C. Wilson, James Tyson, J. Norman Henry, Alfred Stengel, and the late Dr. Arthur V. Meigs.

2 Dohle. *Deutsch. Arch. f. klin. Med.*, 1895, iv, 190.

3 Huchard. *Traité clinique des maladies du coeur et de l'aorte*, Paris, 1899.

4 Dieulafoy. *Clinique médicale de l'Hôtel Dieu*, Paris, 1896-7, p. 71.

5 Gallavardin. *Precis de maladies du coeur et de l'aorte*, Paris, 1908.

6 Fournier. *Traité de la syphilis*, 1899.



igan,<sup>7</sup> and the articles of Allbutt,<sup>8</sup> cover this aspect of the disease in a fairly thorough manner. The more recent lectures of Mitchell Bruce,<sup>9</sup> Schwarz,<sup>10</sup> Breitmann<sup>11</sup> and Goldscheider<sup>12</sup> also contain good clinical descriptions.

The important conclusion of Dohle that syphilis produced a characteristic type of aortitis brought forth some adverse criticism, but no very wide-spread interest, and it was not until the subject was presented before the Deutsche Pathologische Gesellschaft in 1903 by Chiari,<sup>13</sup> Benda<sup>14</sup> and Maichand<sup>15</sup> that arteritis became a common subject for study. During the following years many papers appeared giving anatomical descriptions and statistical records, but as this literature is thoroughly reviewed in Fahr's<sup>16</sup> paper, and in Heixheimer's<sup>17</sup> excellent article, it is unnecessary to do more than refer to these publications. Indeed, the morbid anatomy of the process has been made so familiar through numerous original contributions, as well as by descriptions and pictures in recent text-books such as those of Adam and Aschoff, that it seems scarcely necessary to give more than the briefest outline of the anatomical changes as I have observed them.

#### ANATOMICAL CHANGES

The gross appearances of syphilitic aortitis are in themselves fairly characteristic. The root of the aorta and the arch are most commonly affected, but the process may be found anywhere throughout the length of the vessel. In several instances I have seen an extensive, though circumscribed process in the abdominal aorta. The lesion as a rule is quite sharply confined to a certain area. The smallest areas and probably the earliest which we can recognize consist of well outlined, pale grey, rather translucent elevated, succulent looking patches 0.5 to 2 or 3 cm in diameter. On section the elevated portion of the vessel is translucent and grey, beneath this and corresponding to the media one sees opaque, yellow streaks and patches running the length of the section, and sometimes 1 to 2 mm in thickness. These occasionally sink beneath the level of the knife cut. The larger and more advanced areas form isolated or conglomerate patches 4 to 10 cm in diameter, or completely surround the circumference of the vessels. The distal margin is usually very sharply defined, and beyond this line of demarcation, which may be found somewhere along the arch, the smooth, delicate aorta stretches in wonderfully sharp contrast to the diseased portion. The surface of the larger areas is extremely irregular. The elevated patches mentioned above alternate, or are irregularly intermingled with yellowish, scarred, pitted and seared areas, or with greyish patches that look like thin, crinkled silk. When the process is

7 Corrigan *Edinburgh Med Jour*, 1832, *xxvii*, No 111, 225

8 Allbutt *Allbutt's Syst Med*

9 Bruce, Mitchell *Lancet*, London, 1911, *ii*, 69, 141, 205

10 Schwarz *Centralbl f die ges Therap*, 1911, *xxix*, 225

11 Breitmann *Berl klin Wchnschr*, 1911, *xliiii*, 1763

12 Goldscheider *Med Klin*, 1912, *viii*, 471

13 Chiari *Verhandl d Deutsch path Gesellsch*, 1903, p 137

14 Benda *Verhandl d Deutsch path Gesellsch*, 1903, p 164

15 Maichand *Verhandl d Deutsch path Gesellsch*, 1903, p 197

16 Fahr *Virchows Arch f path Anat* 1904, *clxxvii*, 508

17 Heixheimer *Lubaich Ostertag Ergebn d allg Path u Path Anat*, 1907,

extensive the wall at points is thinned or there may be tiny aneurysmal bulgings no bigger than a pea. When the process is widespread and apparently of long standing, there is an irregular, or diffuse dilatation of the vessel. True saccular aneurysms are common. Not infrequently the changes are marked about the mouths of the branches of the arch. Occasionally this causes distinct narrowing of the innominate or left carotid. Except in the very oldest cases one never sees atheromatous patches containing cholesterol crystals or calcification. When these changes occur they are associated with a typical endarteritis deformans running throughout the length of the aorta. When the process advances to the aortic ring, as it often does, the mouths of the coronary arteries may be partly occluded, or even reduced to a pin hole point, though the lesion rarely extends far into the coronary arteries themselves. With the involvement of the sinuses of Valsalva, and the aortic ring there may be pouching of one and distention of the other so that the circumference of the ring instead of being 5 to 7 cm may reach 9 to 11 cm. The aortic flaps likewise become involved and show a curious thickened and wrinkled appearance which causes more or less retraction and incompetence though in certain cases of typical aortic insufficiency the valves are surprisingly large and pliable while the aortic ring is widely dilated. To this Corrigan himself called attention. Even below the flaps on the endocardium in some instances there are crescentic lines of greyish thickening.

Microscopically the earliest lesions which may be definitely recognized show that all three of the main coats of the aorta are involved. The adventitia shows small accumulations of small round cells about the *vasa vasorum*, and the intima of both arteries and veins may be thickened. Minute blood-vessels extend into the media and are surrounded along their courses by accumulations of plasma cells, small round cells and epithelioid cells. Slight breaks in the elastic tissue are observed in Weigert's stain. The cells of the intima are proliferated and heaped up to form a projection from the inner surface of the vessel.

In the more extensive lesions the perivascular infiltration of the adventitia is very pronounced. The media presents very characteristic areas of coagulation necrosis surrounded and partly infiltrated with plasma cells and small round cells. Giant cells may be encountered. They sometimes contain fragments of elastic tissue. The elastic tissue in special stains is seen to be destroyed, torn and fragmented, and is usually entirely absent in the center of such a patch. The cellular proliferation of the intima is marked. These areas of necrosis or military gummata may be of considerable size, and in two specimens which I have studied they involved not only the media, but large areas in the adventitia, and even the adjacent heart wall, forming true gummata which were readily visible macroscopically. There is frequently a sacculated dilatation of the arterial wall which may vary from a depression scarcely perceptible to a well-formed aneurysm of small size.

The third characteristic picture appears to represent a later stage of the process, and shows a scarred, distorted vessel wall, almost unrecognizable as such, with perhaps complete destruction of all three coats of the artery. Small foci of necrosis surrounded by connective tissue, partly vascularized and infiltrated with varying numbers of plasma cells and small round cells take the place of the media, and extend in marked instances both to adventitia and media, while in appropriate stains the curled fragments of elastic tissue may be seen here and there throughout the lesion.

In certain cases we have found but one of these three types or stages of the process, but as a rule two or all of them are seen in different portions of the vessel walls.

Extending from the root of the aorta the process frequently involves the valves of the aortic orifice and the aortic ring itself. The changes in the valves in such cases consist in localized and diffuse infiltrations of small round cells and plasma cells.

## RELATION OF SYPHILIS TO AORTITIS

That such lesions are in themselves characteristic, and may readily be recognized, is granted by most observers, but that they are always and exclusively due to syphilis is questioned still by many. Evidence is accumulating, however, to show that syphilis is certainly the commonest, if not the exclusive cause. The statistical studies of Marchand, Benda, Herxheimer and Fahr, have been mentioned, and the subject has been collectively reviewed recently by Eich.<sup>18</sup> There is general agreement as to the frequency of a history, or other evidence of syphilis in cases showing this type of aortitis.

More direct evidence was brought forward by Reuter<sup>19</sup> in 1906 who described spirochetes in the walls of an aorta affected by this gummatous process. His observation has been confirmed by Schmorl,<sup>20</sup> Benda<sup>21</sup> and by Wright,<sup>22</sup> who was able to demonstrate spirochetes, often in enormous numbers, in all of five cases of mesoaortitis. From the results of some studies which I have made, and which Dr. Jean V. Cooke undertook at the Pennsylvania Hospital, the presence of spirochetes in these lesions, as might be expected, cannot by any means be constantly demonstrated with Levaditi stains. Portions of the aorta from seven cases of typical syphilitic aortitis, all of which during life had given a positive Wassermann reaction, were stained by the Levaditi method and searched carefully. In three of these, spiral organisms were found in moderate numbers, sparsely scattered through the thickened intima and underlying portions of the diseased vessel wall. That these organisms are *Treponema pallidum* seems almost certain, though actual proof of such by culture from the arterial lesions, a most difficult task, or direct inoculation into animals, has not as yet been accomplished.

Vanzetti,<sup>23</sup> on the other hand, has claimed to produce an arterial lesion in rabbits which simulated syphilitic aortitis in man by the inoculation of bits of syphilitic rabbits' testicles into the sheath of the carotid artery. In from twenty to forty-one days the syphiloma develops about the wall of the vessels. Spirochetes are found only in the adventitia at the seat of inoculation. Though his pictures and descriptions do not convince one that the experimental lesion corresponds precisely with the aortic lesion in man, yet his observation that the first alteration in the vessel wall after perivascular inoculation is a proliferation of intima cells, is of much interest in connection with the histogenesis of the disease in

18 Eich. Frankfurter Ztschr. f. Pathol., 1911, vii, 373.

19 Reuter. München med. Wchnschr., 1906, lvi, 10, 778, Ztschr. f. Hyg. u. Infektionskr., 1906, liv, 49.

20 Schmorl. München med. Wchnschr., 1907, liv, 188.

21 Benda. Berl. klin. Wchnschr., 1906, xliii, 989.

22 Wright. Boston Med. and Surg. Jour., 1909, cli, 539.

23 Vanzetti. Tr. First Internat. Cong. Path., Torino, October, 1911, p. 171.

the human artery, where the lesions in the media are usually attended by a proliferation of the cells of the intima

It remains to be seen, however, whether any other infectious agent may produce the same lesion Klotz<sup>24</sup> has described alterations in the aorta in cases of rheumatic fever in children which bear some likeness to those ascribed to syphilis. In any such studies it is of the utmost importance to exclude the possibility of congenital syphilis, for, as Klotz<sup>24</sup> himself has shown, lesions practically the same as syphilitic aortitis in the acquired disease may be found in infants the subject of congenital syphilis Wiesner<sup>25</sup> and Rach and Wiesner<sup>26</sup> have paid considerable attention to this subject, and have found changes in 59 per cent of the syphilitic fetuses examined These observations have been confirmed by Bruhns<sup>27</sup> and recently by Rebaudi,<sup>28</sup> who, in five cases, was able to demonstrate spirochetes scattered through the aortic lesion Rach and Wiesner state that spirochetes were not once found in any of seven cases These observations afford, besides, strong support to the idea that the disease in adults is due to syphilis

To the above evidence of the syphilitic nature of this process must be added the valuable results obtained from the use of the Wassermann reaction Eich, who perhaps has had the largest series of cases controlled by autopsies, obtained a positive Wassermann reaction in 81.8 per cent of forty-four cases that showed characteristic syphilitic aortitis at autopsy His technic may be criticised, however, since in a number of instances he employed post-mortem blood Pearce<sup>29</sup> collected seventy cases of mesoaortitis from the literature, in 78.5 per cent of which the Wassermann reaction was positive

A question of extreme importance is to determine the time at which the aorta becomes infected It is known that syphilis during the late primary stage becomes a general septicemia, and in certain cases during this period it is possible to demonstrate spirochetes in the circulating blood (Fruhwald,<sup>30</sup> Uhlenhuth and Mulzer<sup>31</sup>) Following this general invasion of the body the spirochetes lodge in different organs and tissues spreading by way of the lymphatics, and it is highly probable that the infection of such organs as the aorta, the nervous system and the liver takes place at this period For some reason, as yet unexplained, the root of the aorta and ascending arch seem to be one of the sites of predilection for the organism Whether or not there are changes in or about the aorta

24 Klotz Jour Pathol and Bacteriol, 1907, xii, 11

25 Wiesner Centralbl f Path u path Anat, 1905, xvi, 822

26 Rach and Wiesner Wien klin Wchnschr, 1907, xix, 521

27 Bruhns Deutsch med Wchnschr, 1906, No 19

28 Rebaudi Monatschr f Geburtsh u Gynak, 1912, xxxv, 681

29 Pearce THE ARCHIVES INT MED, 1910, vi, 478

30 Fruhwald Wien klin Wchnschr, 1912, xxv, 584

31 Uhlenhuth and Mulzer Berl klin Wchnschr, 1912, xlix, 152

during the secondary stage is a question which at present must be left undecided, but it is quite certain that the results of the invasion of the aorta may become manifest soon after the primary infection. Indeed, in the secondary stage of syphilis there may be certain symptoms and signs referable to the cardiovascular system. Fournier mentions palpitation, arrhythmia and tachycardia, but as they occur chiefly in women he ascribes them to functional disorders of the nervous system. Grassmann,<sup>32</sup> in his study of the cardiovascular system of 288 cases of secondary syphilis states that in 85 per cent there were disturbances in the rate or rhythm of the pulse, while in 40 per cent accidental cardiac murmurs usually with dilatation of the heart occurred. Though syphilitic aortitis with its complications—aortic insufficiency, aneurysm, dilatation of the arch and angina pectoris—are usually referred to as late or even parasymphilitic and metasymphilitic affections, there are instances on record in which these conditions have appeared shortly after infection. Harlow Brooks<sup>33</sup> mentions one case in which the perforation of an aneurysm took place before the secondary rash had fully appeared, and another in which a serious aortic lesion, sufficient to cause death, developed within six months of infection. Liek,<sup>34</sup> too, describes a most interesting example in a young man 26 years of age, who developed within seven months after contracting a chancre, dilatation of the aorta visible by x-ray. There were mild anginoid symptoms. Two of my patients died from the effects of syphilitic aortitis four years after the development of a chancre, and such instances are not excessively rare. It seems possible, therefore, that even when the effects of the infection do not make themselves apparent for many years, the actual invasion of the aorta may take place during the secondary stage.

#### CHIEF SIGNS AND SYMPTOMS

Early in the disease, no doubt the involvement of a small portion of the aorta may be of slight immediate significance, but with the extension of the process, there result four grave conditions—diffuse dilatation of the arch, aneurysm, aortic insufficiency and angina pectoris. I have been particularly interested in the association of aortic insufficiency with syphilitic aortitis. In a study of 76 cases of chronic endocarditis that came to autopsy at the Pennsylvania Hospital,<sup>35</sup> 43 cases gave symptoms and signs during life of aortic insufficiency. In about half, or 21 of these, the mitral valve as well as the aortic valve was diseased, and showed retraction or stenosis while the individuals were principally children with a history of rheumatic fever. In none of these was syphilitic aortitis

32 Grassmann *Deutsch Arch f klin Med*, 1900, lxxviii, 455, 1901, lxxix, 58 and 264.

33 Brooks, Harlow *Med Rec*, New York, 1912, lxxxix, 351.

34 Liek *Fortschr u d Geb d Rontgenstrahle*, 1911, xvi, 23.

35 Longcope *Jour Am Med Assn*, 1910, liv, 118.

present In the remaining 22 cases, all of which showed involvement of the aortic valves alone, 18, or 81.5 per cent, were associated with syphilitic aortitis.

With the advent of the Wassermann reaction a valuable method was obtained for the study of these cases of cardiovascular disease, and the astonishing frequency with which syphilis appeared as an etiological factor soon became apparent Citron,<sup>36</sup> in 1908, first reported that of 16 cases of aortic insufficiency, 62.6 per cent gave a positive Wassermann reaction In the next year or so came the reports of Danielopolu,<sup>37</sup> Schutze,<sup>38</sup> Collins and Sachs,<sup>39</sup> Clough,<sup>40</sup> Laubry and Parvu,<sup>41</sup> Deneke,<sup>42</sup> Donath,<sup>43</sup> Oigaaud,<sup>44</sup> Bruchner and Galeseo<sup>45</sup> and Krefling,<sup>46</sup> giving in all, 182 cases of aortic insufficiency, in 135 of which, or in 74.1 per cent, the Wassermann reaction was positive Pearce in 1910, collected the statistics of 57 cases of aneurysm, 38 of which gave positive reactions, 70 cases of meso-aortitis, 57 of which gave positive reactions, and 214 cases of general arterial sclerosis, 29 of which gave positive reactions During the years 1909 and 1910, I<sup>47</sup> made Wassermann tests, using the original Wassermann technique, on 12 cases of aneurysm, 11 of which gave positive reactions, and on 47 cases of aortic insufficiency, 35 of which, or 74.1 per cent, gave positive reactions Of the positive cases, 7 came to autopsy, and all showed typical syphilitic aortitis with involvement of the aortic ring, or of the wall above In the wall of the aorta of three patients spirochetes were found The 10 cases of aortic insufficiency which gave negative reactions were, save one, combined with disease of the mitral valve An autopsy in this one case of pure aortic insufficiency giving a negative Wassermann reaction showed no evidence of syphilitic aortitis Autopsy on the one case of aneurysm which gave a negative Wassermann reaction showed a definite but old scarred syphilitic aortitis

Two of the cases of aortic insufficiency, which gave positive Wassermann reactions, were associated with mitral stenosis One of these came to autopsy, and showed typical syphilitic aortitis involving the aortic leaflets Spirochetes were present in fair numbers in the wall of the aorta There was marked irregular thickening and fusing of the mitral leaflets A nodular, fibrous mass was found on the posterior leaflet The

36 Citron *Beil klin Wehnsch*, 1908, xi, 2142

37 Danielopolu *Compt rend Soc de biol*, 1908, lxi, 971

38 Schutze *Deutsch Ztsch f Clin*, 1908, xxi, 13

39 Collins and Sachs *Am Jour Med Sc*, 1909, cxxviii, 344

40 Clough *Bull Johns Hopkins Hosp*, 1910, xxi, 70

41 Laubry and Parvu *Compt rend Soc de biol*, 1909, lxi, 750, lxvii, 48

42 Deneke *Deutsch med Wehnsch*, 1909, xxxv, 2148

43 Donath *Beil klin Wehnsch*, 1909, xli, 2015

44 Oigaaud *Arch de mal de coeur*, 1910, iii, 478

45 Bruchner and Galeseo *Compt rend Soc de biol*, 1910, lxviii, 74

46 Krefling *Deutsch Med Wehnsch*, 1910, xxxvi, 93

47 Longcope *Bull Ayer Clin Lab*, 1910, No 6, p 60

chorda tendineae were thick and looked as though scarred. Spirochetes could not be found in the mitral lesion. Whether the mitral stenosis was a result of the syphilitic process, or caused by some acute infection, such as rheumatic fever, of which there was no history, could not be determined, but it is evident that mitral stenosis may exist with syphilitic aortitis.

To control the above observations Wassermann reactions were performed on fifty cases, including various types of mitral disease, cardiac hypertrophy secondary to nephritis, and general arterial sclerosis. In the entire series only three positive Wassermann reactions were encountered, two in cases of chronic nephritis with arteriosclerosis, and one in a case of mitral stenosis and insufficiency. This proportion is at least what one might expect in any material collected among adults in a large general hospital.

Since the completion of these studies still other confirmatory reports have been made by Grau,<sup>48</sup> Orkin,<sup>49</sup> Ledermann,<sup>50</sup> Bie,<sup>51</sup> Fiessinger,<sup>52</sup> Jacobsen,<sup>53</sup> Comesatti,<sup>54</sup> Hirtz and Braun,<sup>55</sup> Weintraud,<sup>56</sup> Cummer and Dexter,<sup>57</sup> Goldscheider<sup>58</sup> and others. The percentage of positive Wassermann reactions are variously given for general cardiovascular diseases from 25 per cent to 68 per cent, for aortic insufficiency from 75 per cent to 100 per cent, for aneurysm from 85 to 95 per cent, and for aortic diseases in general, including aneurysm, diffuse dilatation and angina pectoris, from 75 to 88 per cent.

Wolfsohn<sup>59</sup> has recently found that positive reactions to Noguchi's luetin in cardiac disease are even more frequent than the Wassermann reaction. In 12 cases, including 6 of aortic insufficiency, 4 of aneurysm, and 2 of myocarditis, 11, or 91 per cent, reacted to luetin. The one negative reaction occurred in a case of myocarditis. The Wassermann reaction was positive in but 58.3 per cent.

Even from these rather small statistics, confirming as they do the anatomical studies, it may be seen how extremely common syphilitic aortitis and its complications are, and what a large proportion of serious diseases of the cardiovascular system in adults may be dependent on this

48 Grau. *Ztschr f klin Med*, 1911, lxxiii, 292.

49 Orkin. *Berl klin Wchnschr*, 1912, xliix, 1177.

50 Ledermann. *Deutsch Med Wchnschr*, 1912, xxxviii, 1038.

51 Bie. *Ugesk f Laeger*, 1911, lxxiii, No 11, Abstr in *Jour Am Med Assn*, 1911, lii, 1158.

52 Fiessinger. *Bull de l'Acad de méd*, 1911, series 3, lxxvi, 135.

53 Jacobsen. *Deutsch Arch f klin Med*, 1911, clii, 44.

54 Comesatti. *Riv crit di clin med*, 1911, vii, 561 and 581.

55 Hirtz and Braun. *Bull et mém Soc d hôp*, 1911, series 3, xxvi, 363.

56 Weintraud. *Therap d Gegenw*, 1911, lii, 442.

57 Cummer and Dexter. *Jour Am Med Assn*, 1912, lix, 419.

58 Goldscheider. *Med Klin*, 1912, viii, 471.

59 Wolfsohn. *Bull Johns Hopkins Hosp*, 1912, viii, 223.

disease It is evident that most aneurysms of the arch of the aorta, the majority of cases of aortic insufficiency in adults, uncomplicated by mitral disease, many cases of angina pectoris, particularly in individuals under 50 years of age, and a large proportion of cases of dilatation of the aorta are only incidents in the development and progress of syphilitic aortitis, and unfortunately in many instances are the first signs that attract our attention to the disease But it is most important that we should not lose sight of the main and underlying process, and serious as the complications are, our attention should be directed to a study of the diseased aorta rather than to the late manifestations

#### CLINICAL PICTURE

The clinical picture, it is true, is made up principally of the symptoms and signs which accompany these end results, but there are certain features common to all types of the disease the explanation for which is somewhat difficult to give, but which may repay further study To many clinicians the disease has been familiar for years Aside from the well-known descriptions given by Hurhard, Dieulafoy, Gallavardin, Fournier and Allbutt†, the symptomatology and diagnosis have recently been discussed by Mitchell Bruce and Osler<sup>60</sup> in their Lumleian Lectures, and by Breitmann, Schwarz, Goldscheider, Bruhns,<sup>61</sup> Oigaaard,<sup>62</sup> Giau, Flessinger, Oikin and Cummers and Dexter

The 63 cases on which this study is based, include 43 cases of aortic insufficiency, 4 of which were combined with aneurysm, 8 cases of aneurysm alone, and 12 cases of aortitis associated with dilatation of the arch, myocarditis, angina pectoris, or a combination of these conditions The diagnosis was made or confirmed at autopsy in 29 cases, in 10 of these the Wassermann reaction was performed during life and found positive In the remaining 34 cases the Wassermann was positive For the Wassermann reactions in 13 cases which were studied at the Presbyterian Hospital, I am indebted to Dr Albert Lamb In making these tests the Noguchi modification was used In all the other cases I employed the original Wassermann technic

#### AGE INCIDENCE

Most authors have mentioned the fact that these cardiovascular changes due to syphilis are met with in comparatively young people In Bie's statistics the average age at which the symptoms of syphilitic aortitis developed was 42, for aneurysm 50, and for myocardial disease 52 Mitchell Bruce, in a study of 70 odd cases gives the average age at

†Allbutt Lancet, 1903, 11, 139, Brit Med Jour, 1906, 1, 5

60 Osler Lancet, London, March 12 and 26 and April 9, 1910

61 Bruhns Berl klin Wchnschr, 1906, xliii, 513

62 Oigaaard Ztschr f klin Med, 1911, lxxviii, 440



which the first manifestations occurred as 49. Of Cummeis and Dexter's 27 patients, 85 per cent were between the ages of 35 and 55 years. In my own series, the majority of the patients were young, as may be seen in the following table:

Age	Cases	Per cent	Age	Cases	Per cent
20-30	19	30.1	20-40	32	50.7
31-40	13	20.6	20-50	51	80.9
41-50	19	30.1			
51-60	7	11.1			
61	5	7.9			
<hr/>					
63					

Over one-half of these patients were less than 40 years of age, and 80.9 per cent under 50. Almost a third of the patients were under 30 years of age. The youngest patient was a colored woman of 22. At autopsy there was extensive syphilitic aortitis. There were three other patients under 25, all of which came to autopsy and showed extensive syphilitic aortitis. The oldest patient was 68. As a rule, the aneurysms occurred in the older subjects. Except for one case in which a small aneurysm was found at autopsy in a woman of 26, most of the individuals, 10 out of 13, were over 40, and 6 were over 50.

Of the 63 cases, 51 were men, 25, or about half, were negroes. Of the 12 women, 10 were negroes.

It has been generally assumed that the symptoms of syphilitic aortitis develop as a late event in the disease. In Bruce's statistics the average latent period between the time of infection and the onset of symptoms was 25 years, in Cummeis and Dexter's report 17.2 years. Bruce gives the minimum period as 5 years, the maximum as 51. He points out that symptoms in these cases make their appearance about 15 years later than they do in rheumatic fever. Owing to the difficulty in obtaining an accurate history I could determine such data in but 23 cases. Roughly, the average latent period was 16.4 years, very nearly that given by Cummeis and Dexter. The shortest period was 3 years, and there were 4 other cases under 5 years. The longest latent period was 35 years. Bearing on this question of latency is an interesting report by Biermann.<sup>63</sup> Reference has already been made to the changes found in the aorta of congenital syphilitics, and Biermann has recently described a case of congenital syphilis in a girl of 19, who showed dilatation of the aorta with fever. He considers this as an instance of congenital syphilitic aortitis. Wentworth,<sup>64</sup> too, has recently reported a series of Wassermann tests in children among which were five cases of congenital heart disease, two of which gave positive reactions. It is evident that there may be

<sup>63</sup> Biermann. *Deutsch. med. Wchnschr.*, 1911, *xxxvii*, 1157.

<sup>64</sup> Wentworth. *Am. Jour. Dis. Child.*, 1912, *iii*, 363.

syphilitic disease of the aorta which remains latent and gives no symptoms over long periods of time

It is impossible to determine whether any secondary factors acted as predisposing causes in the development of the aortitis. Many of the men were hard working. A history of alcohol, or abuse of tobacco, was not particularly striking. One patient had *tabes dorsalis*. The frequent association of *tabes* and aortic disease is well known, and the question has been thoroughly discussed by Hertz<sup>65</sup>

### SYMPTOMS

The symptoms which have attracted the attention of every one who has written on the subject are pain, dyspnea, often on slight exertion, palpitation and tachycardia. Pain was a prominent symptom in 60 per cent of Bruce's cases. In one-half it was precordial, in the other half anginal in character. Dyspnea occurred in 60 per cent, palpitation in 67.5 per cent. In my series pain of one sort or another, excluding the continuous cervicobrachial neuralgic pains of aneurysm, occurred in 42 cases, or 66.6 per cent, dyspnea in 49, or 77.7 per cent. Palpitation and tachycardia were less frequent.

Pain is an interesting symptom not only because it is so characteristic of this type of cardiovascular disease, but on account of its relationship to the state of angina pectoris, the true nature of which is still so imperfectly understood. It is frequently the first symptom (29 cases), and alone or in combination with dyspnea of various types may be the only symptom for long periods (9 cases). Osler<sup>66</sup> has called attention to the anginoid pain which may precede the appearance of an aneurysm. The cervicobrachial neuralgia, so common in aneurysm, I have not included in this description. The pain is of various kinds. In the majority of cases the patient complains either of a constant or intermittent dull pain beneath the sternum. Sometimes it is described as a painful constriction or oppression, sometimes as a "gripping sensation that comes up from the stomach, and catches at the heart or throat." Mild at first, these disagreeable sensations usually increase in severity, and intermittent attacks become more frequent. In a majority of cases the pains are made worse by exercise. Beginning with mild attacks the patient may one day have a typical paroxysm of angina pectoris accompanied by fear of impending death, and with radiation of pain to the neck, left shoulder, or down the left arm. Rarely the disease starts with severe, typical angina pectoris. Characteristic attacks of angina pectoris occurred in eight of my patients, five of whom had aortic insufficiency. Two patients dropped dead.

65 Hertz. *Les nerfs du coeur chez les tabétiques*, Paris, 1903

66 Osler. *Med. Chron.*, May, 1906

Although the attacks of angina may be free from any disturbances in respiration, very frequently they are closely associated with distinct changes. Occasionally the patient stops breathing in full inspiration, more often there is dyspnea of moderate grade, or attacks of paroxysmal dyspnea, to be described later, accompany the pain so that it is sometimes difficult to distinguish the two. Dyspnea is frequently associated with the milder substernal pain. In the attacks of angina which are free from dyspnea there may be a sharp rise in blood-pressure, in one case from 110 systolic to 170 systolic.

The dyspnea itself is a symptom of the greatest interest, and in one of its forms seems to be highly characteristic of the disease. In the majority of cases there is early dyspnea on slight exertion. In thirty-one cases, or about half, it was one of the first, if not the first symptom. In some cases this slight shortness of breath gradually becomes worse, especially when aortic insufficiency supervenes, until the patient finally shows the constant respiratory difficulty common in broken cardiac compensation. In a second group of cases the dyspnea assumes another and more interesting, though most distressing form. In this group it is paroxysmal in nature, coming on in attacks of five to fifteen minutes' duration. Such attacks were present in nine of my patients, all of whom had aortic regurgitation. These paroxysms may be absolutely the first symptom (seven cases). They vary greatly in number, from two to three during the entire course of the disease, to four or five a day over periods of months. In two cases they occurred daily for almost a year. Though this phenomenon is most common when aortic insufficiency is present, it is seen in cases in which signs of cardiac decompensation do not develop for months, and in one case which is now under observation there have never been signs of decompensation, unless, indeed, these attacks are considered as such. Sometimes the attack is brought on only by exertion but in the majority of cases the paroxysm is absolutely independent of exercise, and not infrequently strikes the patient like a thunderbolt, often while he is asleep at night. Between attacks he is usually able to perform his daily duties. I have observed a number of such attacks in different individuals, and the following notes made at the bedside will give some idea of their nature.

"Suddenly during rounds at 10 40 a. m. the patient showed signs of great distress. He sat up in bed, and gave a sharp agonized cry for help. Going immediately to the bedside he was found sitting up, leaning forward with a pained, anxious expression, and showing the most marked dyspnea. He implored us to relieve him of his distress, but talked quite intelligently throughout the attack, and said there was no actual pain, but terrific difficulty in getting his breath. The supraclavicular spaces were retracted during inspiration, the chest moved scarcely at all, while the respiratory excursions of the abdomen were extreme. Respiration was rapid, and though inspiration seemed difficult, expiration was accomplished with the greatest effort and exertion, and was comparatively much

prolonged. The pulse was 128. The chest was hyperresonant, and on auscultation were heard diffusely scattered sibilant and occasional crackling râles. About the height of the attack the patient began to sweat about the head and face. At this time too, he began to cough, and expectorated a small quantity of thick blood-stained mucus. At 10 45 amyl nitrite was applied, at 10 53 1/100 gr nitroglycerin hypodermatically. During the coughing spell he asked to hang his legs over the side of the bed. He did so, and at 11 05 the feeling of distress disappeared rapidly. The respirations continued, however, to be rapid, and at 11 20, fifteen minutes later, were 35, pulse 108. During the attack the blood-pressure rose from 200 S, 70 diastolic to 247 S, 70 diastolic, to fall in eleven minutes to 178 S, 60 diastolic. At the end of the attack the râles had disappeared over the chest."

Such is the character of these paroxysms, short, lasting often from ten to fifteen minutes, but leaving the patient exhausted for an hour or two afterwards, agonizing, terrifying both to the patient and to the individual who sees him, usually accompanied by an increased pulse-rate, and a rise in blood-pressure that falls rapidly at the subsidence of the attack.

In the attack just described there was no pain, but in some cases there is pain, often excruciating, starting in the substernal region and radiating to the neck, left shoulder and down the left arm. In one case the pain radiated down the right arm. In the severest cases there is usually a cry for help at the start. Some patients remain almost immobile during the paroxysms, others wave their hands and arms about frantically. There is never an attempt to get out of bed or rush to the window. Often there is the fear of impending death. Nitroglycerin has seemed to bring relief.

In the instances that I have watched the dyspnea was distinctly expiratory. The patient could not empty his lungs. During the attacks the chest became emphysematous, and auscultation revealed piping and occasional crackling râles. There was sweating and cyanosis. The attack ended with the expectoration of a little bloody mucus. The agony during some of these attacks is terrific. One patient in whom the dyspnea was associated with angina cut his throat. In two cases the attack itself was fatal.

The condition is very well known. Osler describes it most accurately, and speaks of the condition as one nearly allied to angina—angina of pulmonary type. Oiggaard refers to it as *Luft-Hunger*, to the French it has long been familiar and Huchard terms it paroxysmal dyspnea; by the older authors it is referred to as cardiac asthma, and by some it has probably been considered as acute pulmonary edema. Breitmann calls particular attention to its significance in these cases. Though Huchard as well as many others would definitely exclude these cases from the category of angina pectoris, it is certainly difficult to say in some instances whether the patient is suffering from an attack of angina pectoris with severe respiratory symptoms, or whether he is suffering with paroxysmal

dyspnea with pain, for the attacks vary in different individuals from purely respiratory phenomenon, uninfluenced by exertion, and free from pain, to attacks in which the pain predominates, and in which the paroxysms are definitely associated with exertion. The attacks in their characteristic form simulate very closely a transient severe asthma, an extreme expiratory dyspnea with acute emphysema, and suggest very strongly that the direct cause of the dyspnea is bronchospasm. The possible explanation of the phenomenon can best be discussed when we come to consider the effect of treatment on these symptoms of pain and respiratory distress.

Palpitation is of fairly common occurrence, and may occur early, with this there is sometimes tachycardia. With the development of cardiac insufficiency in the cases of aortic regurgitation or of myocarditis, there naturally ensue the symptoms common to decompensation.

If aneurysm exists the special pressure symptoms dependent on the tumor make their appearance. In eleven of the twelve cases of aneurysm there was pain, usually constant, in the chest, left shoulder, neck and left arm.

As Allbutt has long pointed out, however, these symptoms described above appear most frequently when the sigmoid region is involved, and this has been particularly true in my series. I have also noted that in the younger patients, pain and paroxysmal dyspnea have been most frequent. In seven patients over 50 who had aortic insufficiency, pain was entirely absent in two and very slight in three, the picture in these five cases being almost entirely that of gradual cardiac decompensation. In the remaining two cases there was severe pain and paroxysms of dyspnea.

Finally, it is necessary to mention the possible relationship between the syphilitic aortitis, and certain unexplained fevers in these cases. To this Popoff<sup>67</sup> has recently called attention. He reports three cases of aortic insufficiency with syphilitic aortitis in which there was an unexplained fever that disappeared rapidly after the administration of anti-syphilitic treatment. In Briemann's case of congenital syphilitic aortitis there was fever. Though it is not uncommon to see slight fever or abnormally great variations in temperature in cases of aneurysm and aortic insufficiency with syphilitic aortitis, particularly just after admission to the hospital, it is difficult to exclude in such instances the presence of a slight bronchitis as a cause for the increased temperature. It is interesting, however, to note the effect of treatment on this temperature. In one of my cases of aortic insufficiency, there was a mild unexplained fever reaching at times 101 F, which lasted for eleven days, but disappeared promptly after the first dose of salvarsan. In a second case, fever played a very prominent part in the picture.

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67 Popoff *Ztschr. f. klin. Med.*, 1912, lxxv, 506

## CASE REPORT

A married woman aged 53 was admitted to the Presbyterian Hospital May 6, 1912, complaining of general weakness. She had never been sick before. She had not had any children, the menopause had occurred four months previously. For six months she had been feeling badly weak, and was losing weight. There had been no edema, no pain, no dyspnea, no cough. For six to eight weeks there had been fever with night-sweats. She was an under-nourished, rather pale woman. In both conjunctivae there were small petechiae. The teeth were bad. The lungs were negative to examination. There was some enlargement of the heart, with a faint systolic murmur at the apex, and a double murmur at the base. The liver was palpable two fingers below the costal margin. The spleen could not be felt. There was no edema. The Widal was negative. Leukocytes 8,000, hemoglobin 75 per cent., red blood-corpuscles 4,400,000, 5/11, von Piquet negative, 5/13, Wassermann +++ (Noguchi). From time to time a few petechiae were noted over shoulders and back. Blood cultures made 5/14 and 5/28 gave no growth.

The course of the fever with the injections of salvarsan and Wassermann reactions are shown on the accompanying chart (Fig. 1).

June 13 the patient left the hospital much improved. As the fever did not entirely cease she consulted a physician, who treated her with intramuscular injections of salicylate of mercury. By the middle of July she had improved still further, and was entirely fever-free. She remained afebrile but in September, 1912, suffered a severe break in compensation, from which she died Oct. 18, 1912.

It is of course possible to have an acute bacterial endocarditis or chronic infective process engrafted on a syphilitic aortitis, and two such cases I have followed to autopsy. It is difficult to exclude in this case such a cause for the fever, especially since there were petechiae, a feature so characteristic of subacute or chronic infective endocarditis. Blood-cultures, however, were constantly negative, while the complete disappearance of fever over a period of months would be unusual in infective endocarditis, unless the process had healed—as far as we know, an exceedingly rare occurrence. The gradual decline of fever and general improvement with the very persistent Wassermann reaction under treatment, together with the complete disappearance of fever with prolonged antisyphilitic treatment, suggest very strongly that the fever in this case was really dependent on the syphilitic infection of the aorta.

The early physical signs, unfortunately, are not numerous, and are sometimes difficult of detection, while the outspoken signs usually occur late in the disease.

The earliest, the most important, and the most constant single sign is a positive Wassermann reaction. It is now generally conceded that a positive Wassermann reaction in syphilis means active infection somewhere in the body (Boas<sup>68</sup>). And here I should like to call attention to the possibility and importance of syphilitic aortitis as a cause for positive Wassermann reactions in so-called latent syphilis. From the frequency with which syphilitic aortitis is found accidentally at autopsy, we know that the infection may be harbored in this situation for years without

68 Boas. *Di Wassermann'sche Reaktion*, Berlin, 1910.

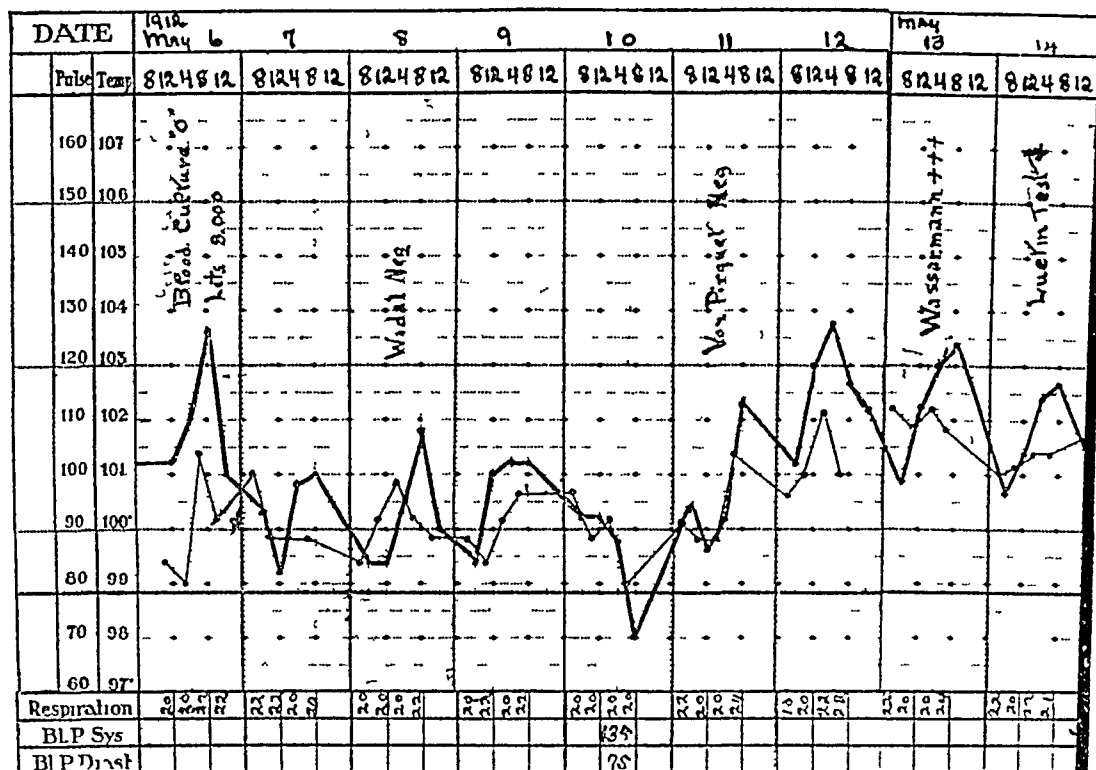


Figure 1—Part 1

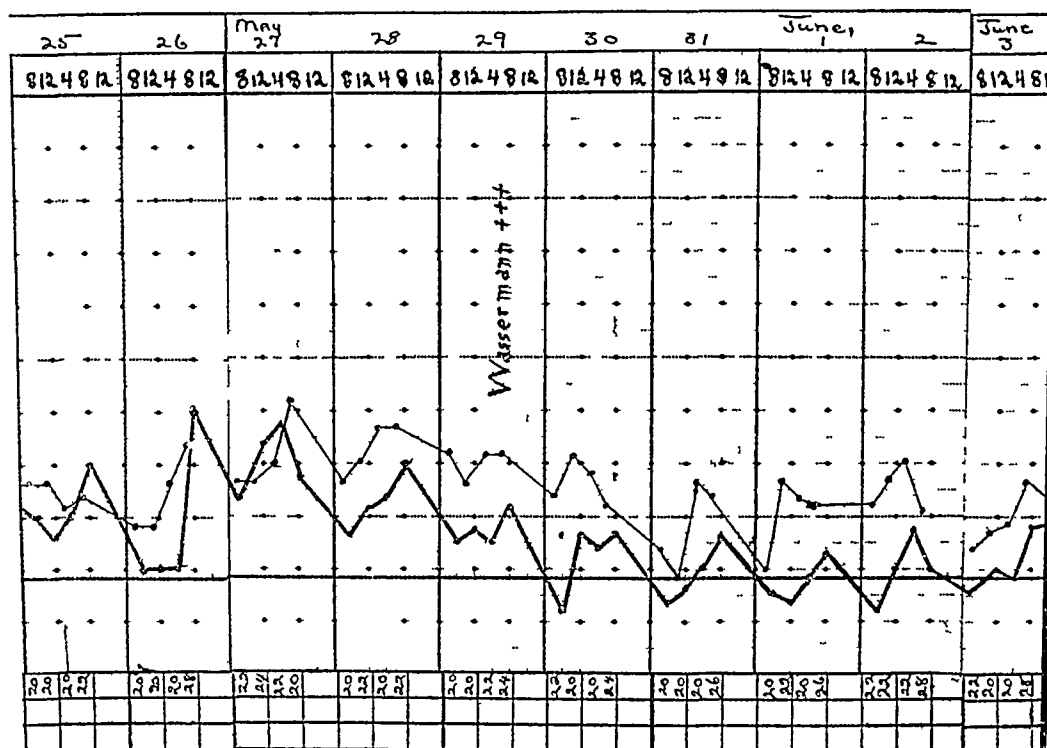


Figure 1—Part 3

Fig 1—Chart showing fever curve and results of Wassermann test in the

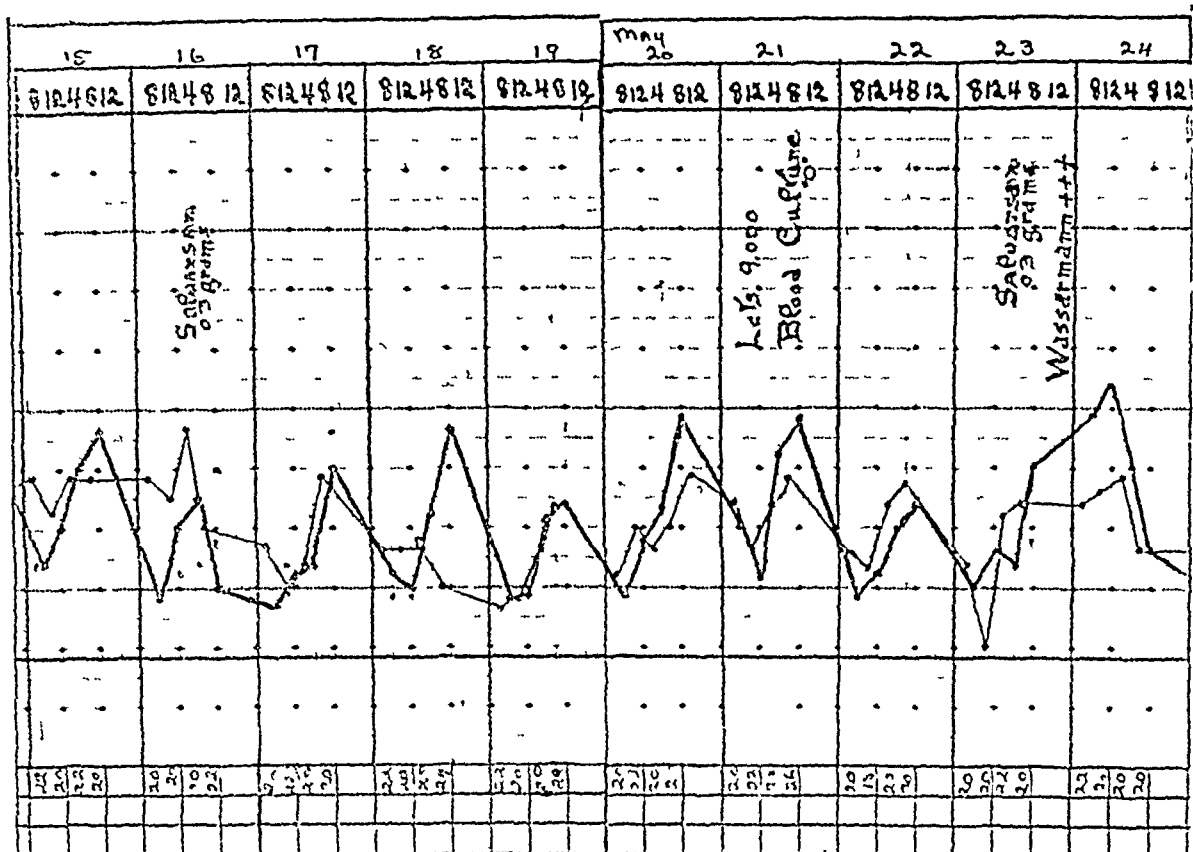


Figure 1 —Part 2

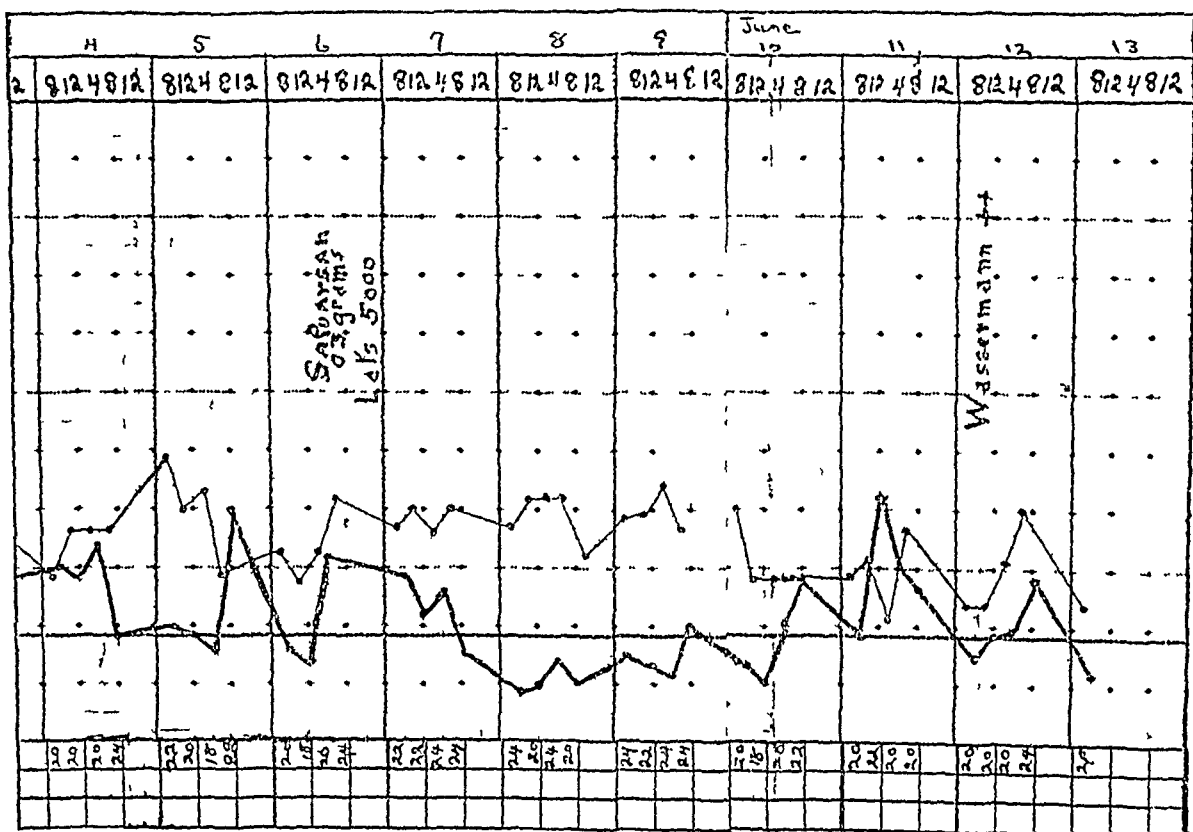


Figure 1 —Part 4

case reported by the author Heavy line = temperature, light line = pulse



detection during life, and indeed it seems as if the root of the aorta might be one of the chief situations in which the infection may lurk. Eich, in his pathological study of 63 cases of syphilitic aortitis, states that in 36, or over half, there were neither signs nor symptoms of the disease during life. One must nevertheless take exception to this statement, for in 9 cases the patients suffered from cardiovascular diseases. Excluding these 9 cases, however, there are still 27, or 42.8 per cent, in which the infection of the aorta was discovered by accident. In 21 out of 30 cases the Wassermann reaction was positive with post-mortem blood. I have now seen a number of cases in which a patch of syphilitic aortitis wholly unsuspected until autopsy, was the only cause which could be found to explain a positive Wassermann reaction during life. This question, of course, needs further investigation before any definite statement can be made but certainly the association is very striking, and probably very frequent. It is therefore of the utmost importance to investigate the cardiovascular system with the greatest care in all cases of so-called latent syphilis that give positive Wassermann reactions. The same statement naturally applies to the nervous system.

Next to the importance of the Wassermann reaction is the condition of the aorta itself. In a certain proportion of cases, but not in all, the lesion leads to a dilatation of the ascending aorta and arch. Dilatation is most common in the older and advanced cases. In 8 of our 35 autopsies there was no dilatation of the aorta. In two cases in which the patients are still living, x-ray examination showed no dilatation. In 25 cases, however, either the x-ray or autopsy disclosed a dilatation of varying grade. This may be uniform or somewhat irregular. For a complete recent discussion of the symptomatology and diagnosis of aortic dilatation one should refer to McCrae's<sup>69</sup> excellent article. One of the most prominent signs is an abnormal pulsation in the subclavian and carotid arteries with an impulse in the episternal notch. In marked instances there is a heave beneath the manubrium or pulsation in the first and second interspaces, usually to the right of the sternum, but sometimes to the left. The veins of the neck are often prominent. In a few instances I have noted a line of dilated veins extending in a semicircle from the first to the third or fourth ribs, and to the right of the sternum.

On palpation a pulsation is often felt in the episternal notch, occasionally a heave and sometimes even a thrill over the manubrium. Percussion gives dulness over the sternum extending either to the right or left of the manubrium in the first and second interspaces. Auscultation very frequently reveals a systolic murmur at the aortic cartilage. The second sound is sharp, ringing, and has the bell-like quality so aptly emphasized by McCrae. This may be present, even in cases of aortic

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69 McCrae. *Am Jour Med Sc*, 1910, vol 469

insufficiency, when the heart sound is accompanied or followed by a diastolic murmur. These sounds are frequently well transmitted over the upper sternal dulness and beneath the clavicles or even into the vessels of the neck. Pressure effects are sometimes noted. There may be a capillary and collapsing pulse even in the absence of an aortic insufficiency.

Of all the methods of physical diagnosis, however, to determine whether or not dilatation exists, the x-ray is the most valuable. The orthodiagraph as pointed out by Vaquez,<sup>70</sup> gives undoubtedly a more accurate picture than the skiagraph or fluoroscopic examination but we

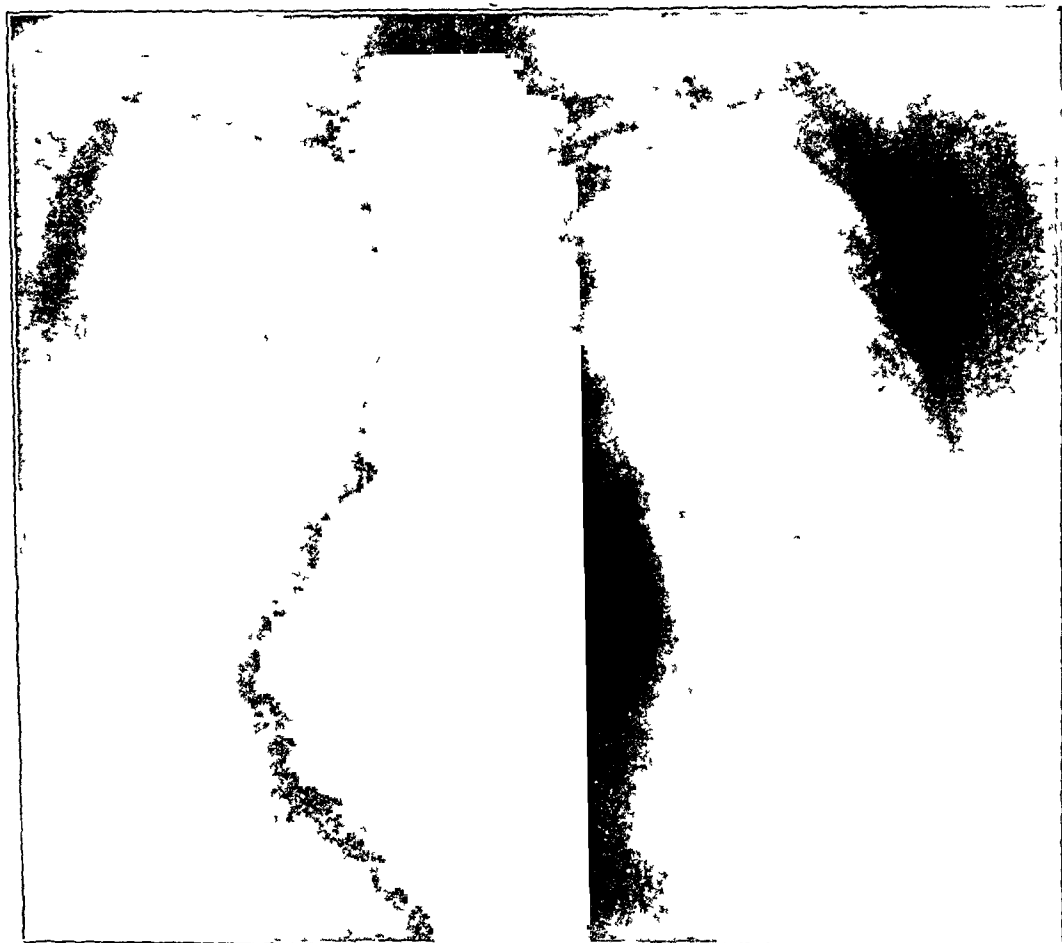


Fig. 2—Case 15. Angina pectoris and aortic insufficiency. Practically no dilatation.

have been obliged to confine ourselves to the latter methods. Fluoroscopy seems indispensable. Examinations have been made with the patient in the prone position and lately it has seemed useful to examine the patient first with the screen on the chest, and then on the back. In the latter position, when the patient lies on his face, the shadow of the heart is not very clear, but the outline of the arch and descending aorta is very distinct, and can be studied with much advantage. The details of the changes in the size and shape of the aortic shadow when dilatation exists

<sup>70</sup> Vaquez. *Arch. d'électr. méd.*, 1911, *xii*, 561.

have been well discussed by Vaquez, and indeed are familiar. The shadow of the normal aorta as seen on the fluoroscopic screen, or in the skiagram lies in its first portion behind the sternum, but at the arch where it curves rather sharply backwards and to the left, there is a well defined rounded knob, seen to the left of the sternum and opposite the second dorsal vertebra. According to the age of the patient and position of the heart, the shadow may show certain slight variations but none which can be confounded with definite dilatation (Fig 2)

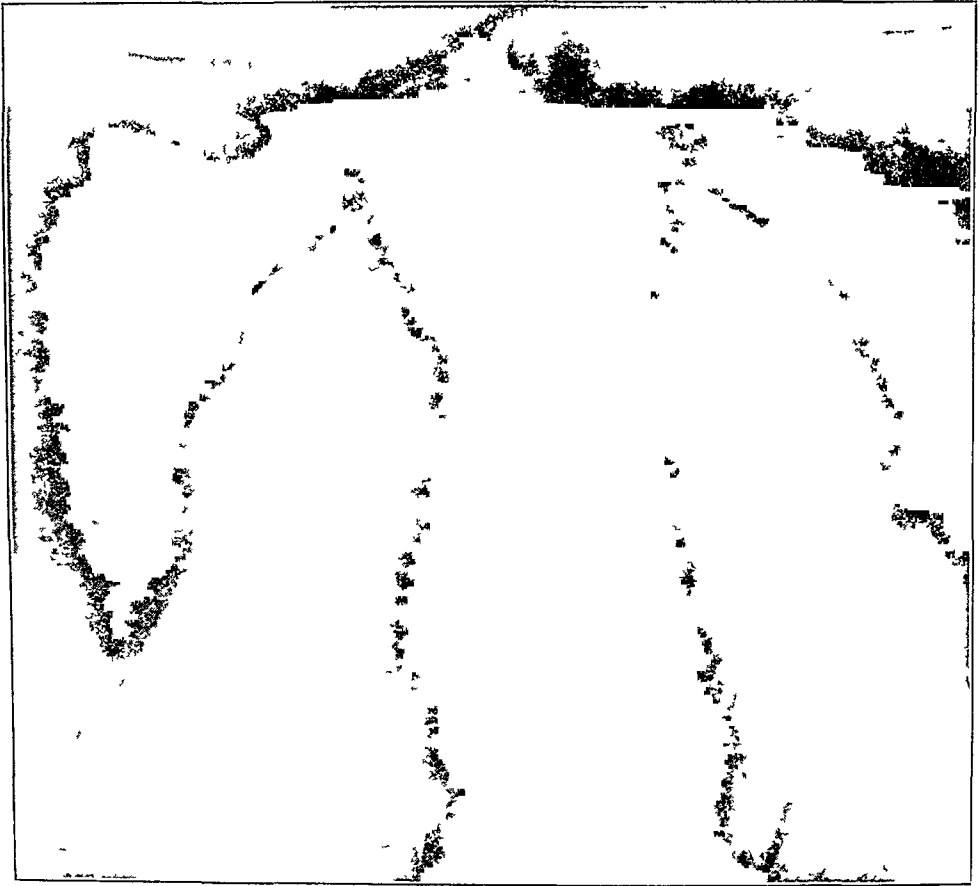


Fig 3—Case 14 Angina pectoris, systolic murmur at base and diffuse dilatation of aorta

The commonest changes that I have observed in dilatation are as follows

First, the aortic shadow as it ascends from the heart shadow is widened so that it projects in a curved line beyond the sternum and reaches to or extends beyond the curved right border of the heart (Fig 3). In most instances the outer shadow is regular, but it may show slight protrusions or bulgings. To the left the normal shadow is broadened. There may, too, be localized irregularities on this outline. In a second group there are alterations of a more or less prominent character in the shadow of the aortic knob, but since this represents the arch it is

unaffected unless the dilatation reaches that far. The commonest abnormality which has been observed is a general enlargement with loss of the well-defined knob shape (Fig 4), instead of which there is a crescentic curve towards the left. In other cases the knob may be enlarged, and its form more prominent than normal (Fig 5). Finally in a third group the aortic shadow appears more or less as a truncated cone with rounded apex and broad base resting on and fusing with the cardiac shadow. In such instances the normal aortic knob is obscured.



Fig 4—Case 10. Aortic insufficiency, paroxysmal dyspnea and diffuse cardiac dilatation.

In any instance but best shown in Figure 3, there may be above the aortic shadow a pyramidal-shaped shadow with base upwards, and beneath the clavicles. This often corresponds to dulness which is obtained beneath the sternal ends of the clavicle. Comparing this shadow with the appearance of the structures in the superior mediastinum at autopsy, it seems to represent the dilated great arteries as they arise from the arch, and course

upwards. In almost any case, but not frequently, the heart may assume a position more nearly horizontal than normal.

Though syphilitic aortitis commonly results in more or less dilatation of the aorta, it is not of course the only cause, so that diffuse dilatation does not in itself form sufficient basis for a diagnosis. In aortic insufficiency following rheumatic fever there may be marked permanent dilatation without the presence of macroscopic lesions in the aorta, save perhaps a thinning of its walls.

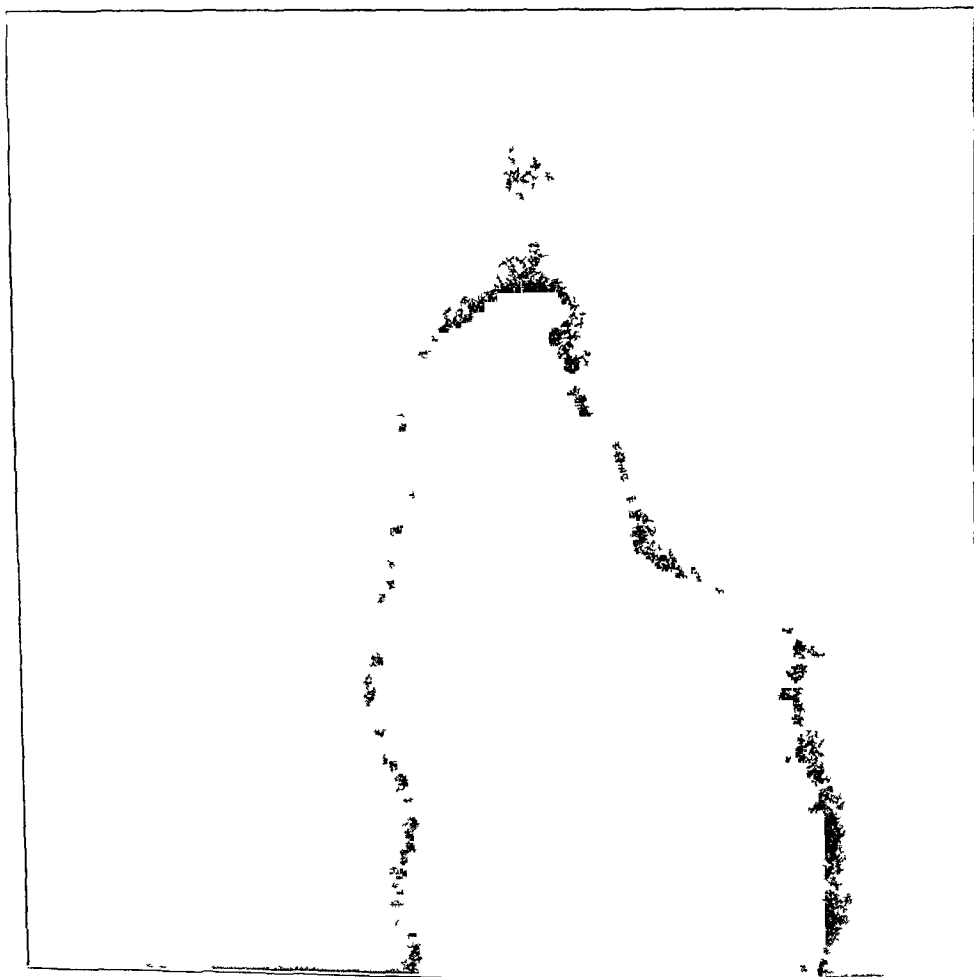


Fig. 5—Case 11. Syphilitic aortitis, dilatation of aorta, prominence of aortic knob.

The importance of the presence of aortic insufficiency and aneurysm have been sufficiently emphasized, unfortunately they appear as a rule late in the disease.

Some increase in the size of the heart is usually found in all cases whether aortic insufficiency exists or not. With the marked enlargements there are as a rule loud systolic murmurs at the apex. In one case, however, there existed only a presystolic gallop rhythm.

The pulse in the majority of instances is regular, and we have not noted any characteristic qualities, though in one instance a markedly collapsing pulse and capillary pulse existed without any other signs of aortic insufficiency. Occasionally the patches of aortitis, which not infrequently are situated about the mouths of the great vessels, become sufficiently extensive to narrow their lumen, or even to occlude them, in which event the pulse in the two radials or carotids show inequalities in size and force. In one case the pulse in the left common carotid was completely obliterated. Occlusion of the opening of the vessel was found at autopsy.

The prognosis, at least in cases which are seen in general hospitals, is bad. In 24 fatal cases in Bruce's series the average duration of life was 5.2 years. In my series there were 38 fatal cases. Of these, 4 patients succumbed to acute infections not directly connected with the aortitis. In the remaining 34, death took place in 23, or in 67.6 per cent, within a year and a half of the onset of symptoms and in 9, or 26.4 per cent, within six months of onset of symptoms. The most rapid culmination took place in one case in a few weeks, 2 patients died within two months, the most prolonged case lasted about six years. Of the 25 patients who are known, or are supposed to be living, the disease has existed in 9 for two years, in 4 for three, in 4 for four, in 1 for five and in 4 for six years. Of the 38 fatal cases, 8 patients died suddenly in an attack of angina pectoris, or paroxysmal dyspnea, 3 died of acute infectious diseases, and the remainder succumbed to cardiac failure.

In some cases, particularly the advanced ones, the diagnosis is made with ease and certainty, but in others with the greatest difficulty. The commonest symptoms and signs are substernal pain, or angina pectoris, slight dyspnea on exertion, or attacks of paroxysmal dyspnea, evidence of a dilated aorta, and enlargement of the heart. A combination of any, or all of these with aortic insufficiency in a man or woman about or below middle life, is characteristic, while a positive Wassermann reaction assures the diagnosis in practically every instance. The mere presence of an aneurysm of the arch or root of the aorta presupposes in almost every instance syphilitic aortitis.

The history of severe rheumatic fever in a young man with aortic insufficiency, who gives a positive Wassermann reaction, may well lead to confusion, and unless pain or paroxysmal dyspnea be present, it would seem well-nigh impossible to come to any conclusion as to the etiology of the aortic lesion. I have seen two such cases in which an exact diagnosis could not be made. Since the Wassermann reaction is one of the most constant evidences, it may, and indeed should, be the first indication to put the physician on his guard, and suggest in cases of so-called latent syphilis the most careful examination of the cardiovascular system.

TABLE OF COLLECTED CASES OF SYPHILITIC AORTITIS

	Name	Admitted	Sex	Color	Ages	Syphilis	Duration of Illness	Symptoms
	M	6/16/11	F	C	39	?	1 year	Aching in chest and back, later spells of shortness of breath, lately edema
	H	4/14/11	M	C	49	Denies	16 mos	Began with dyspnea on exertion, slight cough, oppression in chest, four days before admission sudden severe pain in chest, violent dyspnea, cough, fulness in stomach, edema
3	B	4/13/11	M	C	68	Denies	3 years	Cough, swelling of feet 6 mos, dyspnea, slight pain in chest, blind spells
4	D	1/17/11	M	W	48	Denies	1 year	Sense of constriction about chest, pain in left side of neck and down left arm, no dyspnea or edema
5	M	11/28/10	M	W	41	16 years	1 year	Pain in chest and back, severe and constant Lost 20 lbs in weight
6	L	9/13/10	M	C	35	Denies	5 weeks	Attacks of dyspnea and smothering sensation, palpitation, late edema, rapidly worse
7	Mc	7/29/10	M	W	33	15 years	9 months	Pain in chest, shortness of breath on exertion Later angina with dyspnea during attack, edema
8	M	11/25/10	M	C	39	4 years	5 months	Pain in chest, coming on with exertion radiating to left shoulder No dyspnea No edema
9	R	11/11/10	M	C	46	29 years	11 months	Slight dyspnea on exertion, paroxysmal dyspnea with pain, edema of feet for 8 mos
10	H	10/22/11	M	C	28	Denies	2 months	Paroxysms of dyspnea with sense of constriction in chest No edema

TABLE OF COLLECTED CASES OF SYPHILITIC AORTITIS—(Continued)

Diagnosis	Wass. Mann	Salvaisan	Reaction	Entire Duration of Disease	Remarks
Aortic insufficiency, no dulness over sternum	6/17++++	6/24, 0.3 gm intraven	None	1 yr 8 mos Dead	Death, Feb 12, 1912 autopsy Slight return of symptoms later, with pain
Aortic insufficiency, cardiac insufficiency, diffuse dilatation of aorta x-ray	4/20++++ 5/24 neg	4/26, 0.25 gm intraven 5/20, 0.3 gm intraven	None None	1 yr 10 mos Living	Marked improvement Temporary loss of ability to work again 6 mos later decomposition without pain
Aortic insufficiency broken cardiac compensation	4/18++++ 5/24++++ 6/7+++ 6/21++	4/28, 0.3 gm intraven 5/20, 0.3 gm intraven 6/10, 0.3 gm intraven	None Chill Nausea	3 years +	Improvement marked 5/20, pain in chest gone, 5/26 has pain in chest Decomposition on rest and dig hosp feeling well gone
Dilatation of aorta (x-ray), slight aortic regurgitation, enlarged liver, anginal pain	1/24++++	2/10, 0.6 gm intramusc	Fever	2 yr 10 mos + Living	Much improved Aug working hard, feeling well
Dilatation of aorta (x-ray) Heart normal, anginal pain	1/30++ 2/15—	12/8, 0.6 gm intramusc	Slight	3 yrs + Living	Greatly improved Permanent Gained weight, Aug working as fireman
Aortic insufficiency Dilatation of aorta, severe broken compensation	10/14++++	11/14, 0.45 gm intramusc	Local	5 months Death	Very slight temporary improvement Sudden death Autopsy Syphilitic aortitis involving aortic valves, pseudobulbar pneumonia Sections of aorta different from other cases
Aortic insufficiency Dilatation of aorta (x-ray), very slight edema, angina pectoris, S P 170, D 70	9/16++++	11/21, 0.45 gm intramusc	Local	1 yr Death	Marked temporary improvement Anginal attacks 3-4 times daily before salvarsan Two wks after treatment much better Sometimes only one attack in 3-4 days By 12/28, recurrence Suicide Autopsy Dilatation of aorta aortic insufficiency
Aortic insufficiency, angina pectoris, S P 120, D 80	11/30++++ 12/21++ 1/10/11+++ 2/7++	11/30, 0.6 gm intramusc	Local	8 mos Dropped dead	No definite relief from angina Death, 2/1/1911
Aortic insufficiency Paroxysmal dyspnea with pain Broken compensation S P 178 D 90	11/14++++ 12/21++ 1/10+ 2/28+ 3/3— 3/24+ 4/12++	11/16, 0.5 gm intramusc	Local	1 yr 5 mos Death	Marked temporary improvement Before treatment, attacks every day and night for 11 mos For 2 weeks after, one attack The following 2 wks recurrence followed by complete freedom with ability to get about for 2 months Later recur with death
Aortic insufficiency Dilatation of aorta (x-ray) Paroxysmal dyspnea Slight fever S P 118 D 82	Noguchi 10/26++++ 11/1++++ 11/8++++ 11/15++++	11/2, 0.3 gm intraven 11/13, 0.3 gm intraven 11/22, 0.3 gm intraven	None None None	1 yr + Living	Improvement permanent Complete disappearance of paroxysmal dyspnea and fever Well Nov, 1912



TABLE OF COLLECTED CASES OF SYPHILITIC AORTITIS—(Continued)

	Name	Admitted	Sex	Color	Ages	Syphilis	Duration of Illness	Symptoms
	N	11/ 8/11	M	C	40	20 years	5 years	Pain in chest, acute, radiating to left arm, 1 yr shortness of breath on slight exertion, edema, cough
	N	12/ 1/11	M	W	61	Denies	6 years	Palpitation, slight dyspnea, angina pectoris
	T	12/17/11	M	W	47	28 years	9 months	Pain in chest at first Two violent attacks of dyspnea, palpitation general weakness, no edema
4	B	3/ 2/12	M	W	51	25 years	2 3 years	Dyspnea slight on exertion Angina pectoris for 1 year
5	T	3/20/12	M	W	36	19 years	1 year	Angina pectoris on exertion or excitement
16	W	8/ 2/12	M	W	68	Denies	4 months	For 4 mos attacks of dyspnea pain over heart radiating to left shoulder, 3 wks, edema One transient attack of blindness
	R	5/ 6/12	F	W	53	?	6 months	Weakness, loss of weight, fever
18	C	9/ 9/12	F	C	38	+	6 months	Palpitation, shortness of breath, pain over heart, occasionally attacks of dyspnea at night
19	L	9/11/12	F	W	39	?	9 months	Attacks of angina with dyspnea on exertion, 5 days edema
20	Mc	8/31/12	M	W	50	9 years	8 months	Dull pain in left shoulder, constant, later down left arm 4 mos dyspnea, 1 mo aphonia

TABLE OF COLLECTED CASES OF SYPHILITIC AORTITIS—(Continued)

Diagnosis	Wassermann	Salvarsan	Reaction	Entire Duration of Disease	Remarks
Dilatation of aorta (x-ray), anginal pain, broken compensation, enlarged heart with mitral insufficiency S P 105 D 65	11/15+++ 12/8— 1/26— 3/22—	11/24, 0.3 gm intraven 12/1, 0.3 gm intraven 12/8, 0.3 gm intraven 12/16, 0.3 gm intraven	None None None None	6 yrs + Living	Complete disappearance of pain. Repeated attacks of broken compensation. Doing fairly well.
Angina pectoris. No dilatation of aorta (x-ray) S P 150 D 104	12/10++	12/29, 0.3 gm intraven	Slight	6 yrs 6 mos + Living	Greatly improved. Still doing well.
Aortic insufficiency. Aneurysm of arch of aorta (x-ray) S P 184 D 70	12/8+++ 12/20++ 1/12— 8/20—	12/8, 0.3 gm intraven 12/15, 0.3 gm intraven In next month 2 doses 0.3 gm intraven	Slight	1 yr 6 mos Living	Improved. No symptoms. Gained strength. Syntomatically well.
Dilatation of arch of aorta (x-ray), systolic murmur at base, slight cardiac hypertrophy, tabes dorsalis angina S P 130 D 90	3/28+++ 4/3++	3/28, 0.2 gm intraven 4/5, 0.3 gm intraven 4/14, 0.3 gm intraven	None None None	3 yrs + Living	Well up to the present time, working.
Aortic insufficiency. No dilatation of arch (x-ray) Angina pectoris	5/23++ 5/29—? 6/13±	5/23, 0.3 gm intraven 5/29, 0.3 gm intraven 6/6, 0.3 gm intraven 6/20, 0.3 gm intraven 7/15, 0.6 gm intraven 9/13, 0.6 gm intraven 9/25, 0.6 gm intraven	None None None None None Vomiting	1 yr 5 mos Dead	Improvement with temporary cessation of attacks after each dose. Herxheimer reaction. Sudden death Oct 1, 1912.
Aortic insufficiency aortic dilatation (x-ray) Paroxysmal dyspnea with pain S P 186 D 58	6/23+++	8/24, 0.3 gm intraven	Slight	4 mos Death	Sudden death within 4 hours of salvarsan.
Aortic insufficiency, fever, anemia	5/11+++ 5/23+++ 5/29+++ 6/12++	5/16, 0.3 gm intraven 5/23, 0.3 gm intraven 6/6, 0.3 gm intraven	None None Vomited	11½ mos Death	Moderate improvement. Loss of fever after injections of Hg. Death Oct 12, 1912, of cardiac decompensation.
Aortic insufficiency, dilatation of aorta S P 165 D 60	9/13+++	9/19, 0.3 gm intraven	Fever	6 mos Living	.....
Aortic insufficiency, dilatation of arch (x-ray) Attacks of angina and dyspnea S P 155 D 50	9/20+++	9/13, 0.3 gm intraven 4/20, 0.3 gm intraven	None Slight	9 mos Living	Improvement. For 4 days before salvarsan 7 attacks. In next week attacks.
Aneurysm of aorta (x-ray), differences in pulses, paralysis of left vocal cord, pressure on left bronchus	9/6+++ 9/13++	9/7, 0.3 gm intraven 9/13, 0.3 gm intraven 9/20, 0.3 gm intraven 9/28, 0.3 gm intraven 10/8, 0.3 gm intraven	None None Slight	8 mos Living	No improvement.

## TREATMENT

Since the recognition of the syphilitic origin of certain cardiovascular diseases, antisyphilitic treatment has been recommended and used with varying degrees of success (Huchard, Fournier, Osler, Allbutt). It is usually stated that such treatment may bring about relief from pain. Within the last few years, however, more particular attention has been paid to the treatment of these cases. Goldscheider thinks that the outlook is poor. Potassium iodid is insufficient and must be combined with mercury or salvarsan. Oigaard, on the other hand, reports rather satisfactory results with the use of mercury and iodid. In this manner he has treated fifteen patients with marked improvement in all cases. This benefit showed itself by the disappearance of substernal pain, angina and paroxysmal dyspnea, in increasing strength and returning ability to work, and an improvement in the anemia when this was present. The relationship which he found to exist between the Wasseimann reaction and disappearance of symptoms is interesting. In six cases the Wasseimann test became negative during the first cure, which lasted about three months, in the remaining cases the reaction disappeared more slowly, and only after two or three courses of treatment. In three instances there was a return of symptoms while the Wasseimann was still negative, while in four the symptoms disappeared before the Wasseimann.

With the introduction of salvarsan, Ehrlich's original warning against the use of this drug in the presence of cardiovascular disease prevented for some time its employment in syphilitic aortitis, but now sufficient data have accumulated to show that the danger under such conditions is slight. Breitmann, who collected the cases of death after salvarsan injections, reported in the literature, has discussed this question quite fully from a theoretical standpoint. He thinks the drug may prove dangerous when there is disease of the coronary arteries.

The experimental work of Auer<sup>71</sup> has shown that salvarsan injected intravenously in acid solution is dangerous. Rabbits and dogs injected intravenously with 0.5 per cent acid solutions develop cardiac dilatation, and show abrupt fall in blood-pressure with immediate death. The intravenous injection of 0.5 per cent alkaline solution in dogs seems to have little effect on the blood-pressure, and no marked effect on the heart, though its factor of safety may be so reduced in some instances that an extra strain brings on fibrillation and death. With higher dilutions of the drug, even acid solutions may be harmless when injected slowly. The alkaline solution employed by Auer is five times as strong as that used for man in whom 0.1 per cent solutions are employed. Hoke and Rihl,<sup>72</sup>

71 Auer. THE ARCHIVES INT. MED., 1911, viii, 169, Jour. Exper. Med., 1911, xiv, 248.

72 Hoke and Rihl. Ztschr. f. exper. Path. u. Therap., 1911, ix, 332.

who experimented with intravenous injections of 0.5 per cent salvarsan in alkaline solution state that such a solution will lower the blood-pressure in rabbits, but that this is principally due to its effect on the central nervous system, and not on the heart and blood-vessels directly.

From a practical standpoint the use of salvarsan in syphilitic aortitis seems to be comparatively harmless, though later I will point out a possible source of danger when large doses are given, and the main point at issue is as to whether it is of real benefit. Weintraud<sup>50</sup> has reported the results of treatment by salvarsan of twenty-six cases of syphilitic heart and arterial disease. The cases included aortic insufficiency, angina pectoris, myocardial disease with syphilitic arteritis and sclerosis of the cerebral arteries. He has not seen any ill effects from the injections. Two to four injections of 0.2 to 0.5 gram were given. In many of the cases there were no symptoms, or where symptoms were present they were so mild that any benefit derived from the injections could not be estimated. In only three cases, all of aortic insufficiency with angina, could he be sure of improvement. Others, too, have used salvarsan in isolated instances, but give little information as to its value (Fliessinger, Goldscheider, Biermann, Hirtz and Braun, Schminke<sup>73</sup>).

Salvarsan has been given to 20 of my series of cases. Among these there were 14 of aortic insufficiency, 9 of which were associated with angina pectoris, or attacks of paroxysmal dyspnea, one of these latter having an aneurysm as well. 5 cases of aortitis associated with true angina, anginal pain or cardiac enlargement, and 1 case of aneurysm.

The drug has been given for the most part intravenously, but in 6 cases it was used before the intravenous method of administration became general, and was then given by the Lesser method intramuscularly. Three of these patients received intramuscular injections of 0.6 gram, 2 received 0.45 gram, and 1, 0.5 gram. The remaining 14 cases have usually been given several doses of 0.3 gram intravenously. In this manner of divided dosage 4 cases have received 0.3 gram each, 2 cases 0.6 gram each, 4 cases 0.9 gram each, 1 case 1.2 gram, 1 case 1.8 gram and 1 case 3.0 grams. The doses have been given usually at intervals of eight to ten days. Salvarsan reactions have not been very common. Severe reactions with chills, fever and vomiting or diarrhea have occurred only six times in the thirty-seven administrations. During the last year freshly distilled water has always been employed.

In choosing the dosage I preferred to administer small amounts repeatedly, rather than one or two full doses, and after my rather limited experience this attitude seems justifiable, for it is possible that there is some danger in giving large doses, particularly in patients with angina pectoris and paroxysmal dyspnea.

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73 Schminke *Reichs Med Anz*, Leipz, 1911, xxxvi, 513, 545

Although death has occurred in eight of the twenty cases, in only one instance could it be even remotely connected with the injection. This one patient suffering from aortic insufficiency, and severe attacks of paroxysmal dyspnea and anginal pain, died suddenly within forty-eight hours of the first intravenous injection of 0.3 gram. Even this may have been a coincidence, for on another occasion a patient with angina died suddenly on the day before the first injection was to be made. Cardiac decompensation alone certainly does not seem to be a contra-indication. Seven patients were in a critical condition from decompensation when the first dose was given. Except in the case just described, if any effect was produced it was improvement.

All of the fatal cases suffered from aortic insufficiency. Four patients died of cardiac failure, one three weeks, three six months after treatment, one patient died of angina pectoris seven months after treatment, while one patient committed suicide one month after treatment.

In only one case (No. 6) was it possible to obtain an autopsy. The patient was in a hopeless state of cardiac decompensation when 0.45 gram of salvarsan was injected intramuscularly. He died three weeks later. Autopsy showed the typical gross appearance of syphilitic aortitis. Microscopically the lesion in the aorta appeared perhaps somewhat less cellular than the average, but did not differ materially from the lesions which have been seen in a number of other cases.

#### SUMMARY

The twenty treated cases have been summarized in the accompanying table (Table 1). It may be said once and for all that I have observed no definite beneficial effect on the cardiac incompetency itself, nor has there been any change in the anatomical condition. Signs of aortic insufficiency have not been reduced, nor have aneurysms grown smaller. And, indeed, when one comes to draw conclusions relative to the effect of certain therapy in a group of cases, the symptoms of which are so manifold and so varying, I am aware that the most extreme precautions are necessary. In such a small group, too, coincidences may deceive one, and I have therefore attempted to preserve as critical an attitude as possible.

It has, however, been impossible to escape from the fact that certain of these patients have been benefited by salvarsan treatment, and this after all is not especially surprising, for these individuals must be regarded as suffering not only from a mechanical defect in the circulatory apparatus, but as well from a localized chronic infection. Thus it is reasonable to suppose that if this infective process is ameliorated, or cured, the general condition of the patient will likewise improve. In most instances this has been the case. The majority of patients feel considerably better after one or two injections. The patients who have

improved sufficiently to go back to work report that they feel stronger and better than they have for years. Few, however, have gained weight, though the appetite increases.

The most striking result, however, has been the effect of treatment on the pain and attacks of paroxysmal dyspnea. In all but four cases, there has been permanent, or marked temporary or immediate improvement in this condition. In five cases there has been up to the present time permanent relief of pain. Two of these patients (Nos 4 and 5) had suffered for one year when first observed. At the present time, two years after treatment, they are well and working hard. One patient (No 14), who had suffered constantly from angina pectoris for two or three years, is well and working seven months after treatment. The fourth patient (No 13), with aortic insufficiency, aneurysm and occasional attacks of paroxysmal dyspnea, is well and working hard six months after treatment, and in the fifth case (No 11), though there has been repeated decompensation, pain of anginal nature which had existed for five years, has recurred but once over a period of ten months.

In six cases there has been most striking temporary improvement. Two cases (Nos 7 and 9) that had suffered for about a year with paroxysmal dyspnea accompanied by excruciating anginal pain, obtained complete temporary relief. This lasted in one instance for two months during which time the patient was able to go about and do a little work. At the end of this time the attacks recurred, became progressively worse and the patient finally died. In the other case the improvement of much the same nature, lasted only about four weeks. In another case (No 2) there was relief from pain for six months. At the end of this time the pain recurred, and since then the patient has had almost constant decompensation. In one most striking case of angina pectoris (15) lasting over a period of one year, with sometimes six and eight attacks a day, there has been almost, or indeed entire relief for periods of three weeks to a month after the injections of salvarsan, during which time the patient could attend to his daily work. At the end of this time the attacks recurred, gradually becoming more frequent and more severe, until he finally returned to the hospital for treatment. Occasionally he only remained in the ward one or two days, and twice only one night, so that the effect of rest or diet can be excluded. A second patient with angina pectoris (No 12) left the hospital much improved and remained well for four weeks. Later he was lost sight of. Finally, a woman who had attacks of angina for nine months almost daily, and on any slight exertion, improved immediately while in the hospital, but later had a recurrence. During four days before salvarsan was given there were seven attacks. During the next two weeks after two doses of 0.3 gram of salvarsan, there were but two attacks.

In the remaining cases there was one patient with aortic insufficiency with severe broken compensation (6), who was apparently unaffected, one of severe angina pectoris and aortic insufficiency (No 8), who, after one intramuscular injection, showed no definite improvement, and died during an attack. One patient (No 16), already described, who died forty-eight hours after the first injection, while the pain in one case of aneurysm with cervicobrachial neuralgia was uninfluenced after four intravenous injections of 0.3 gram. The remaining five cases improved considerably during their stay in the hospital, but have either been under observation too short a time to say what the result will be, or have been lost sight of.

In the study of these cases one fact has been very strongly impressed on me, and that is the persistence of a positive Wassermann reaction, or the rapid return of a positive reaction after a temporary abatement during treatment. There were eleven cases in which the Wassermann test could be repeatedly performed. In four of these only has it been possible to obtain, so far, a persistently negative reaction. All four cases showed marked improvement in symptoms (Nos 2, 5, 11 and 13). In the cases (Nos 9 and 15) it has diminished in intensity coincident with a relief in symptoms only to return again and become strongly positive with the recrudescence in one instance of attacks of paroxysmal dyspnea, and in the other of angina pectoris. In the latter case the reaction was still positive, even though 3 grams have been given. In five other cases it has remained positive after the injection of 0.9 gram intravenously, and in one case after the injection of 0.6 gram intravenously. But the first relief of symptoms, even though temporary, has come soon after the first or second injection in most instances, and while the Wassermann reaction was still positive.

Thus the improvement in symptoms manifests itself very rapidly, and usually within four to six days after the injection. We have, however, noticed an interesting phenomenon in a number of instances, namely, an increase in severity of symptoms within twenty-four to forty-eight hours after intravenous injections. This has been most striking in cases of angina pectoris and paroxysmal dyspnea. During the day or two following injections the paroxysms of dyspnea or attacks of angina increase in severity and number, then rapidly diminish and entirely disappear. This was most striking in one case of angina pectoris that received on three occasions 0.6 gram intravenously. A careful record was kept of the number of attacks during these periods and the accompanying chart (Fig. 6) illustrates the characteristic effect.

I cannot but feel convinced that treatment by salvarsan does have a distinctly beneficial effect on the pain and paroxysmal dyspnea in syphilitic aortitis, but as I have had more and more opportunity to study these cases, it has become increasingly evident that a cure is exceedingly

difficult to accomplish. But the very rapid amelioration of the pains, attacks of angina pectoris and paroxysmal dyspnea is not only important for the patient, but perhaps suggests certain explanations for these symptoms. So closely are the attacks of paroxysmal dyspnea associated with angina pectoris in this group of cases that here at least I prefer to consider them together.

I am aware that many explanations have been offered to account for the phenomena, and the theories of angina pectoris are legion. The frequent occurrence of lesions about the sigmoid region, and in the immediate vicinity of the coronary arteries, has led most observers to

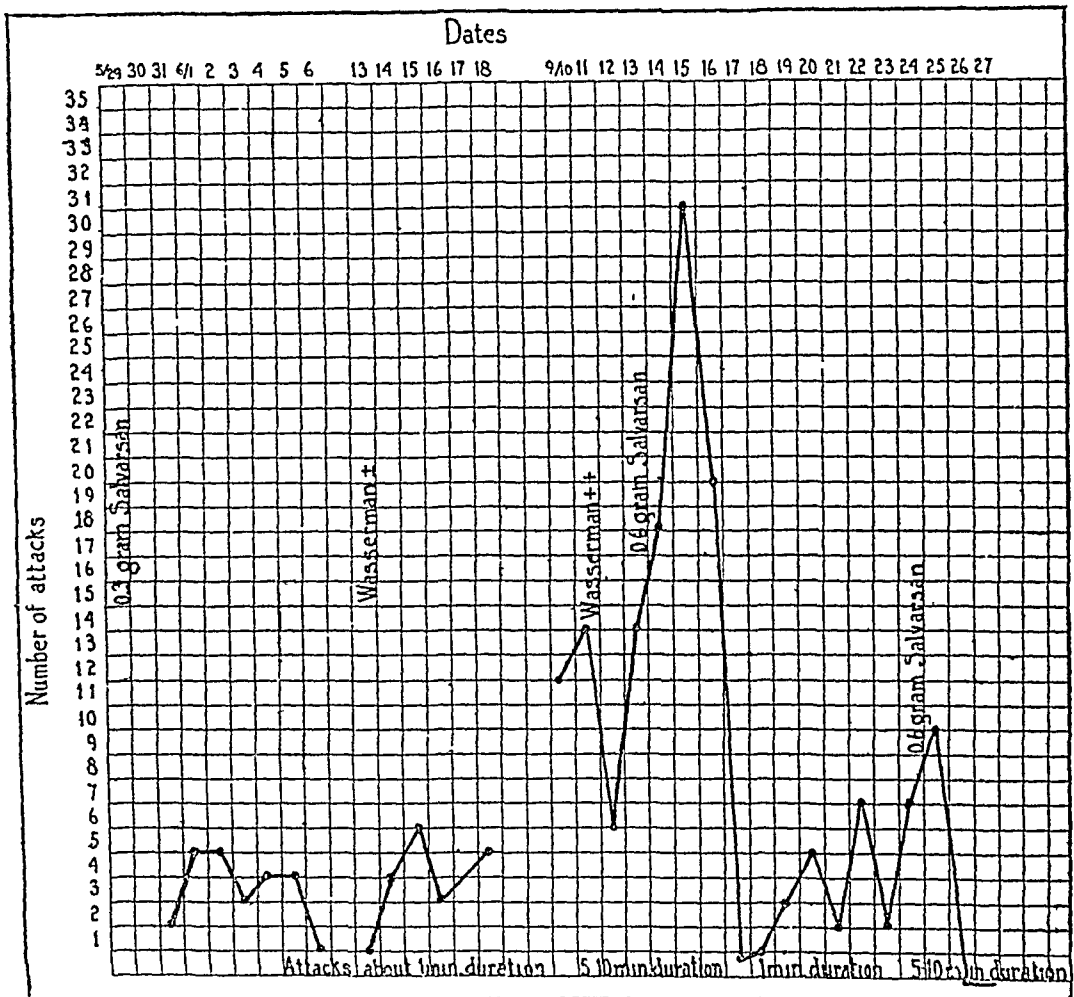


Fig 6—Chart with curve showing the number and duration of attacks of angina following the intravenous administration of salvarsan in a case of angina pectoris

infer that disturbances in coronary circulation in this class of cases was responsible for the attacks of angina pectoris, and, perhaps, the attacks of paroxysmal dyspnea as well. The conditions, however, are complicated. One has to deal with an active infection at the root of the aorta to which the nerve supply is rich, and where in consequence disturbing reflexes may be excited, frequently involvement of the coronary circulation, and in a large proportion of instances, actual insufficiency of the aortic valves with the resultant changes in pressure in the left ventricle and then effects. It is impossible here to discuss the subject of angina



pectoris I need only refer to the works of Huchard, Rosenbach,<sup>74</sup> Osler,<sup>75</sup> Von Neusser<sup>76</sup> and Mackenzie<sup>77</sup>

We have not in the least been able to convince ourselves from autopsies in these cases that there was any direct association between disease of the coronary arteries and attacks of angina pectoris or paroxysmal dyspnea. Almost complete occlusion of the mouths of the coronary arteries has been found without either symptom appearing during life, and attacks of angina and paroxysmal dyspnea have occurred in cases which at autopsy showed large coronary arteries with wide mouths.

That these attacks may be associated with acute distention of the ventricle is possible, since all have occurred in cases of aortic insufficiency, but certainly such attacks are much more common in syphilitic aortitis than in aortic insufficiency caused by rheumatic fever.

The study of my cases, however, has suggested very strongly that these symptoms are closely associated with the inflammatory reaction at the root of the aorta, and are directly dependent on it. The fact first that symptoms may increase temporarily in severity following intravenous injections of salvarsan, and that the most pronounced reactions have occurred with the largest doses lends support to the idea that this represents, as it were, a Heixheimer reaction, and that the increase in symptoms is due to the increased reaction of the tissues towards the liberation of toxin in excess from rapidly destroyed spirochetes. Following this there is rapid subsidence of symptoms, so rapid, indeed, that it could scarcely be ascribed to very great modification in anatomical structure. There might, however, be rapid improvement in the inflammatory reaction. Finally, the temporary relief of symptoms with severe recurrences could best be explained by associating the symptoms directly with the progress of the inflammation.

The paroxysmal dyspnea, as I have already suggested, simulates very closely an attack of asthma, and on account of the sudden onset, the violent type of expiratory dyspnea with suffocating sensations, the acute emphysema, and rapid subsidence, it impresses one as an acute temporary bronchospasm. That such an explanation holds for many cases of true asthma, seems most probable. Indirectly, too, the recent experiments of Januske and Pollak<sup>78</sup> have some bearing on the question, for they have been able to offer an explanation for the beneficial effect of epinephrin in asthma. They found that the marked bronchospasm caused by the injections of muscarin or peptone in animals was promptly relieved by injections of epinephrin and less rapidly, but more permanently by atropin. Pal,<sup>79</sup> too, has reported that such substances as epi-

74 Rosenbach. *Die Krankheiten des Herzens*, 1897.

75 Osler. *Angina Pectoris*, 1897.

76 Von Neusser. *Angina Pectoris*, 1909.

77 Mackenzie. *Lancet*, London, 1895, 1, 16.

78 Januske and Pollak. *Arch f exper Pathol u Pharmacol*, 1911 lvi, 205.

79 Pal. *Deutsch med Wchnschr*, 1912, xxxviii, 5.

nephrin, atropin, caffein and the nitrites which act as vasodilators to the coronary arteries, produce a dilatory effect as well on the bronchial musculature. Recently Park,<sup>80</sup> by direct experiment, has confirmed these results obtained with epinephrin. In the cases of paroxysmal dyspnea nitroglycerin, as mentioned before, seems to have some effect in cutting short the attack, and in cases which have been watched for days or even weeks in the wards before salvarsan was given it was the only drug which seemed to have any influence. It is possible that, if it had any effect at all, it is through a relief of bronchospasm, and not from its action on the coronary arteries. Atropin has been employed a few times, but not sufficiently often to say anything regarding its action. Epinephrin I have feared to use.

Having still more important bearing on this subject are some old experiments of François Frank<sup>81</sup> on aortic reflexes. By irritating the inner surface of the aorta of dogs he was able to produce quite constantly certain respiratory phenomena. These consisted of three types: (1) Sudden apnea with the respiratory muscles in spasm either during the inspiratory or expiratory phase, or apnea with general inhibition of all respiratory movements, (2) tachypnea, without severe constitutional symptoms, and (3) a slow dyspnea of severe and grave form. The cause of this dyspnea he showed quite plainly was spasm of the bronchial musculature. He believed, too, that there was coincident contraction of the pulmonary artery. Associated with this type of dyspnea was a contraction of the peripheral vessels and rise of blood-pressure. Occasionally a spasm of the laryngeal muscles occurred. In other cases he was able to produce all the signs of aortic insufficiency (the capillary and collapsing pulse) save a diastolic murmur through irritation of the root of the aorta and without injury to the sigmoid valves. Stewart<sup>82</sup> has observed this last phenomenon and considers it as a reflex from the root of the aorta, and in some experiments in which aortic insufficiency was performed on dogs I have repeatedly confirmed this observation. That Frank's respiratory phenomena have not been noted since is almost certainly due to the method of experimentation, for in Stewart's experiment, and in those which others have performed, full ether anesthesia or artificial respiration was employed.

It is thus evident that disturbing reflexes may be set up experimentally in animals by irritation of the root of the aorta, and there is no reason to suppose that the same thing should not be true for man. The dyspnea caused by bronchospasm, and the contraction of the peripheral arteries producing heightened blood-pressure in the experimental animal

<sup>80</sup> Park *Jour. exper. Med.* 1912, xvi, 568.

<sup>81</sup> Frank, François *Arch. de Physiol.*, 1890, series 5, 11, 508 and 547, *Jour. de Anat.*, 1877, xiii, 545.

<sup>82</sup> Stewart *THE ARCHIVES INT. MED.*, 1908, i, 102.

is a close reproduction of the paroxysmal dyspnea as it occurs in syphilitic aortitis, and it seems quite justifiable to suggest that the two conditions are the same. It would be difficult to explain the increase in blood-pressure which occurs during these attacks in man on the presence of pain, or of cyanosis, for pain is frequently absent and dyspnea may continue for some time (fifteen to thirty minutes) after the sudden drop in blood-pressure which comes with the relief of acute symptoms. Our observations, therefore, seem to lend strong support to the idea that these symptoms are dependent on a reflex generated at the root of the aorta by the syphilitic inflammatory process.

Hoover<sup>83</sup> has recently called attention to certain respiratory phenomena which he believes are associated with disturbances of the vagus nerve. In two cases there were attacks of paroxysmal dyspnea and acute emphysema associated in one with an inflammatory mass in the mediastinum, and in another with aneurysm of the arch of the aorta. In both these cases the vagi were found at autopsy involved in the tumor masses. In two other cases of aortic insufficiency there occurred attacks of tachypnea associated with slow pulse. Both patients were relieved by atropin.

Though there is no positive evidence other than the results of treatment that the cases of angina pectoris as well as those of paroxysmal dyspnea in this group are of reflex origin, the definite Herxheimer reaction combined with the rapid improvement and later recurrences suggest that the actual inflammation of the wall of the aorta is of great importance in determining the onset of these attacks. The immediate cause of the attacks of angina may of course be constriction of the coronary arteries, but the true etiology probably lies in the diseased aorta, and not in the coronary arteries themselves.

There are not lacking those who have regarded angina pectoris as a reflex depending on reflex nerve impulses. Nothnagel's<sup>84</sup> theory of angina pectoris vasomotoria is well-known. Huchard, though recognizing that inflammations about the root of the aorta might cause a reflex angina pectoris from involvement of the nerves, would exclude such cases from the category of true angina pectoris. Recently this whole question has been discussed by Hertz.<sup>85</sup> Actual disease of the cardiac plexuses has been described by Benenati<sup>86</sup> in two of three cases of syphilitic aortitis with angina pectoris, but others have not been able to confirm these findings. It does not seem necessary, however, to presuppose such lesions, since involvement of the nerve endings in the root of the aorta might be sufficient to determine the onset of reflexes.

The question, of course, complicated as it is, should be put to experimental proof before going further, but the suggestion that these attacks

83 Hoover Jour Am Med Assn, 1911, lvii, 1733

84 Nothnagel Deutsch Arch f klin Med, 1867, iii, 309

85 Benenati Riforma med, 1902, ii, 326

of paroxysmal dyspnea and angina pectoris in this particular class of case are directly connected with the syphilitic inflammation at the root of the aorta, and that these symptoms are of reflex nature rather than dependent on anatomical lesions of the coronary arteries, seems in accord with my observations

The permanent relief of these symptoms can only be obtained, if at all, by the most persistent treatment. It is probably difficult to reach the spirochetes by the blood-stream, so that the diseased aorta is hard to attack. I have been more and more impressed with the necessity of giving repeated doses of salvarsan, and am now not as much discouraged by recurrences as at first. It may be that neosalvarsan will prove more efficacious, or the combination of salvarsan with injections of mercury. Salvarsan, however, would seem to be the best method of primary attack, since the symptoms which may be relieved are immediately dangerous to the life of the patient. The possibility of producing a Herxheimer reaction in cases with paroxysmal dyspnea and angina pectoris should be constantly borne in mind, and in such instances full doses might bring about an alarming immediate increase in symptoms or sudden death.

#### CONCLUSIONS

Syphilis produces a characteristic lesion of the aorta, which is responsible, as is shown by autopsy statistics and the Wassermann reaction, for most aneurysms, about 75 per cent of cases of aortic insufficiency in adults, many cases of dilatation of the aorta, and a certain group of cases of angina pectoris.

The infection of the aorta probably takes place during the secondary stage, and though the symptoms and signs of syphilitic aortitis with the complications may develop within a few months of infection, the process usually remains latent, or unrecognized for an average of sixteen to seventeen years. Thus, syphilitic aortitis is probably a common cause for the presence of a positive Wassermann reaction in so-called latent syphilis.

The early symptoms and signs of syphilitic aortitis are a positive Wassermann reaction, precordial pain, slight dyspnea, attacks of paroxysmal dyspnea and angina pectoris, cardiac hypertrophy, increased pulsation of the vessels of the neck and signs of dilatation of the aorta.

The precordial pain, paroxysmal dyspnea and angina pectoris are temporarily or permanently relieved by repeated injections of salvarsan, but in certain instances these symptoms, especially after large doses, may be aggravated for the first forty-eight hours after injection.

The paroxysmal dyspnea, which may be regarded as acute bronchospasm, and possibly the angina pectoris in syphilitic aortitis is dependent on the inflammatory reaction in the wall of the aorta, and may be regarded as reflex disturbances set up by the syphilitic process involving the root of the aorta.

## THE MINUTE VOLUME AND ALVEOLAR AIR IN PULMONARY EMPHYSEMA

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This discussion will deal with two phases of pulmonary emphysema which have to do with the lung as a respiratory organ quite apart from the respiratory threshold, minute-volume of blood passing through the pulmonary circulation and influences from the peripheral nerve supply of the respiratory organs

Patients who apparently have the same degree of emphysema behave in different ways. One of my patients had pronounced cyanosis, a respiratory rate of 16 to 18 per minute, a minute-volume of respired air of 8 liters.  $\text{CO}_2$  content of his alveolar air was 8.55 per cent. This patient did not suffer from an hunger and never had an asthmatic attack.

The second patient presented two phases. On admission to the hospital he was cyanotic. The respiratory rate was 14 per minute. The minute-volume of respired air was from 8 to 10 liters. The alveolar air contained 7.2 per cent of  $\text{CO}_2$  and an hunger was pronounced. A few days later conditions improved. He no longer suffered from an hunger, but the respiratory rate was 15 per minute, the minute volume of respired air was 6.380 liters. His alveolar air contained 5.3 per cent of  $\text{CO}_2$  and cyanosis had disappeared. At first glance one would say the lung ventilation was much better during the first period and therefore the real difficulty consisted in an impairment of the lung as the organ of external respiration, i. e. the lung did not afford a good medium for the interchange of carbon dioxide and oxygen between the blood and alveolar air. But we will see later in the discussion the real difficulty did not consist in an impairment of the respiratory function, but in the ventilation function. Thus far my observations have been made on cases of marked emphysema which differed much in the clinical symptoms of cyanosis, an hunger and minute-volume of respired air. But when this external respiration was investigated it was found that the patients all suffered from impaired ventilation, but reacted differently. A significant clinical test carried out on the patients substantiates this explanation. None of

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\* Read at the meeting of the Association of American Physicians, Atlantic City, May, 1912

these patients showed the slightest modification of their symptoms when they breathed an atmosphere of pure oxygen. In other words they were not suffering from a low oxygen content, but from a high carbon dioxide content of their alveolar air and this can be ascribed only to impaired ventilation.

Patients who suffer from an impairment of the external respiratory function must of necessity get relief from the inhalation of oxygen. This is very clearly demonstrated in pulmonary edema and bronchopneumonia of children, whose cyanosis is instantly relieved by the inhalation of oxygen, when the real difficulty is impaired ventilation throughout the entire lung. In my personal experience I have known only one patient who got relief from the inhalation of oxygen, and I did not have the opportunity of confirming that. I have only the patient's personal testimony and that must be received with caution from emphysematous and asthmatic persons.

The significance of pathological changes in the alveolar walls of atrophic emphysematous lungs seems very doubtful in all of the cases I have studied. Inhalation of oxygen is a good clinical method of differentiating between these two functions, viz., external respiration and lung ventilation.

The early observations on the first patient were made with the aid and direction of Dr. J. J. R. Macleod in the physiological laboratory. I wish here to express my thanks and acknowledge the debt of gratitude I owe him for his active aid and instruction in the use of the physiologist's methods of studying respiration and for many helpful suggestions.

The method used in studying alveolar air is that described by Haldane and Priestly<sup>1</sup>. Specimens of the tidal air were procured by Zuntz's method, and the analyses of the respired air were made with Haldane's modification of Petterson's<sup>2</sup> apparatus.

The first patient was a man 46 years old, 5 ft. 6 in. high, and weighing 140 pounds when these observations were begun in December, 1910.

The patient had pronounced cyanosis of the lips, nose, ears, tongue and fingers. Drumstick finger tips were marked. The patient denied ever having had any attack of asthma or experiencing the sense of air hunger. His persistent complaint was a sense of fullness and slight pain over the frontal region and a sense of fullness and pressure in the epigastrium. There was moderate cough and very little expectoration. At this time in 1910 the patient worked as presser in a garment factory and suffered no inconvenience at his work on account of the emphysema.

The heart's apex was in the sixth interspace and the left border of the heart extended 14 cm. to the left of the median line in the sixth interspace. The right cardiac border extended 6 cm. to the right of the median line in the fourth interspace. There were no murmurs nor accentuation, nor palpable thrills or palpable closures from any of the heart's valves. The veins of the neck and upper extremities were rather large but no abnormal venous pulsations were visible. There

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<sup>1</sup> Jour. Physics, XXII, 227

<sup>2</sup> Petterson Ztschr. f. Analyt. Chem., XXV, 467

were no signs of any impairment of the mass movement of blood and Dr G N Stewart<sup>2</sup> estimated the mass movement through the hands, and found it quite normal according to his method

The lungs were very emphysematous. The lower borders were at the ninth rib in the axillary line on both sides and filled the pleural sinus posteriorly.

The costal angle was not enlarged during inspiration and the anterolateral portion of the thoracic wall from the sixth to the ninth ribs, inclusive, were drawn toward the median line during inspiration. The epigastrium was protruded but the lower end of the sternum was drawn toward the vertebra. From a posterior view one sees, however, a distinct increase in the transverse diameter of the base of the thorax in the plane of the posterior axillary line. When the diaphragm occupies a low position the following phenomena are observed during respiration: Retraction of the lower end of the sternum, a narrowing or a want of enlargement of the costal angle and approximation of the hypochondria and protrusion of the epigastrium. These signs were always very pronounced in this patient for the two years he was under observation. Auscultation revealed the characteristic prolonged expiratory murmur and in abundance of coarse and medium dry and an occasional moist râles during inspiration and expiration.

The patient had a moderate cardiac enlargement without any signs of disease of either the pulmonary or aortic arterial systems. No signs of mediastinal disease or disease of the pericardium. The minute volume of blood was normal.

The striking feature about this patient was the cyanosis without dyspnea and without any indication of cardiovascular disease.

The alveolar air was estimated a great many times over a period of sixteen months and the  $\text{CO}_2$  content was never lower than 7.5 per cent and was most of the time between 8.1 per cent and 8.5 per cent.

October 14, 1911, the following four analyses were made of the alveolar air:

- 1  $\text{CO}_2$  = 8.35 per cent  
    $\text{O}_2$  = 11.70 per cent
- 2  $\text{CO}_2$  = 8.99 per cent  
    $\text{O}_2$  = 12.70 per cent
- 3  $\text{CO}_2$  = 8.2 per cent  
    $\text{O}_2$  = 12.41 per cent
- 4  $\text{CO}_2$  = 8.55 per cent  
    $\text{O}_2$  = 11.04 per cent

The cyanosis and partial pressure of  $\text{CO}_2$  in the alveolar air sustained a very constant relation to each other. January 20, 1911, when he was able to be at work and had pronounced cyanosis the alveolar air contained in two analyses 7.3 per cent and 7.5 per cent of  $\text{CO}_2$ . December 11, when he was admitted to the hospital complaining of headache and a sense of pressure in the epigastrium and had too a marked increase of the bronchial symptoms and intense cyanosis, the alveolar air contained 9.7 per cent of  $\text{CO}_2$  and 10.73 per cent of oxygen.

On the former occasion when the  $\text{CO}_2$  content of the alveolar air was 7.5 per cent the respiratory rate was 18 per minute and the minute volume was 8.530 liters.

On the latter occasion when cyanosis was much more intense the respiratory rate was 19 per minute, the  $\text{CO}_2$  content of the alveolar air was 9.7 per cent and the minute-volume was 8.530 liters. He not only tolerated a high  $\text{CO}_2$  content of the alveolar air at all times but tolerated an increase from 7.5 per cent to 9.7 per cent without any hunger or any material change in the rate or minute volume of respiration. This is a striking result when compared with the intolerance of  $\text{CO}_2$  in normal persons, and also when compared with the tolerance of an increase in the  $\text{CO}_2$  of the patient's alveolar air, after forced breathing and attempts at holding the breath to the breaking point.

<sup>3</sup> Stewart, G N. Heart III, 33 and 76.

March 17 1911 the following experiments were made

The alveolar air of Drs Macleod, Wyckoff and myself contained the following

J J R M	= 5.67 per cent $\text{CO}_2$	C F H	= 5.1 per cent $\text{CO}_2$
C W	= 5.8 per cent $\text{CO}_2$	Patient Sam B	= 8.1 per cent $\text{CO}_2$

We then took the alveolar air of each at the breaking point after holding the breath as long as possible with the following results

J J R M	= 6.71 per cent $\text{CO}_2$	C F H	= 6.71 per cent $\text{CO}_2$
C W	= 7.27 per cent $\text{CO}_2$	Sam B	= 9.0 and 9.7 per cent $\text{CO}_2$

Sam B then breathed as deeply and as rapidly as possible twenty times in 30 seconds, a period of apnea for 18 seconds followed. Then with the resumption of automatic respiration the alveolar air contained 9.4 per cent of  $\text{CO}_2$ . Another time Sam B breathed twenty-five times in 30 seconds. Apnea for 18 seconds followed and with the resumption of automatic respiration the alveolar air contained 10.28 per cent of  $\text{CO}_2$ . Nine months later when his cyanosis was very intense he did not suffer from air hunger (19 respirations per minute), and the percentage of  $\text{CO}_2$  in the alveolar air had attained a percentage which equalled his maximum endurance on the former occasions when the  $\text{CO}_2$  in his alveolar air was 8.1 per cent during tranquil breathing.

There was another point of interest in Sam B relative to his high respiratory threshold. He never had apnea when awake, but when the inhibition of sleep was added to his ordinarily high respiratory threshold, apnea ensued. In this instance, as in instances of slumber apnea associated with sclerosis of the cerebral arteries, the apnea occurred in light sleep. Jan 27, 1911, Dr Macleod took a tracing of Sam B's respiration in the pneumograph constructed after Haldane's design. The accompanying tracing shows periods of apnea (Fig 1). In the tracing the upward stroke marks the expiratory excursion. In watching the tracing we were at first much concerned to see the cessation of respiration, but as the apnea recurred it was observed respiration ceased as the patient's eyelids closed in sleep. We had repeated opportunities to observe this fact. It was interesting to see the upstroke of the lever to the abscissa mark the expiratory phase of the thorax as the eyelids fell in sleep. Unlike the slumber apnea of arterial disease the apnea was not followed by hyperpnea and air hunger. As the apnea ceased and the patient simultaneously awakened and resumed automatic respiration the rate and rhythm and depth of the respiratory excursions were resumed as they were up to the moment of apnea.

On the day the tracing in the pneumograph was taken Sam B's alveolar air contained 7.5 per cent, 7.9 per cent and 8.0 per cent of  $\text{CO}_2$  in three analyses. His minute-volume of respired air was 7.9 liters.

Dec 15, 1911, Sam B's alveolar air contained 9.59 per cent  $\text{CO}_2$  and 10.09 per cent of oxygen. Cyanosis was much more pronounced than on



the day the pneumograph tracing was made. When his cyanosis was so pronounced and his alveolar air contained 9.59 per cent  $\text{CO}_2$ , he would lie in bed and go to sleep for short intervals of five or ten minutes. It was common for him to go to sleep five or six times in an hour, but when he went to sleep he did not cease breathing. It seems the partial pressure

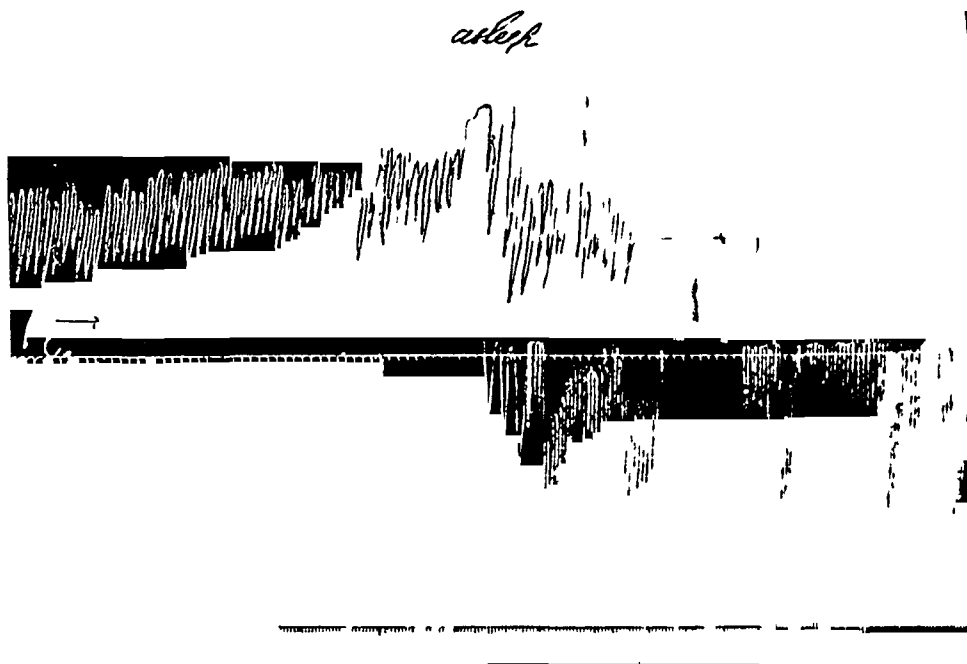


Fig 1—Read from left to right. The upstroke marks the expiratory excursion. The arrests of respiration in the expiratory phase mark the points at which the patient went to sleep.



Fig 2—Read from left to right. The upstroke marks the expiratory excursion. Note that oxygen in solution did not modify the respiration, whereas the excursions increased the instant some carbon dioxide was introduced into the respired air.

of  $\text{CO}_2$  was so high that apnea was never allowed in his moments of slumber. During this period his respiratory rate was 27 per minute, but the minute-volume was only 6.566 liters. When asked if he suffered from

a sense of an hunger he always protested that he had no difficulty in breathing and said his only trouble was headache and a sense of pressure in the epigastrium. The man was really suffering from carbon dioxide poisoning. During the winter and spring we repeatedly gave him large amounts of oxygen to breathe, and although the partial pressure of oxygen in the air he breathed was as high as 50 per cent., it never modified the respiration in any way.

We have in this patient a heightened respiratory threshold with an alveolar air rich in  $\text{CO}_2$  and poor in oxygen, without hyperpnea and with a normal minute-volume of respired air. The lung ventilation is therefore apparently but not really good.

The tidal air was then estimated according to Zuntz's method and the alveolar air was analyzed at the same time. It is clear that the  $\text{CO}_2$  given off must come from the alveolar air and, as Haldane suggests, if we know the minute-volume of respired air and its content of  $\text{CO}_2$  and also the content of  $\text{CO}_2$  in the alveolar air, then we have a formula for estimating the proportion of alveolar to tidal air. I have a minute-volume of 8.16 liters. This minute-volume of air contains 3.28 per cent of  $\text{CO}_2$  and my alveolar air contains 5.05 per cent of  $\text{CO}_2$ . We have the formula

$$\frac{3.28 \text{ times } 8.16 \text{ liters} = 5.05}{3.28 \text{ times } 8.16} = \text{alveolar air} \\ \text{therefore} \frac{\quad}{5.05}$$

Dec 8, 1911, the Zuntz apparatus was used for collecting a sample of air from Sam B.

Time of collection=10.25 min

Rate of respiration=12 per min

Minute-volume=9.16 liters

Zuntz specimen  $\text{CO}_2$ =4.23 per cent or 0.387 L per min,  $\text{O}_2$ =17.45 per cent

Alveolar air  $\text{CO}_2$ =8.3 per cent,  $\text{O}_2$ =10.9 per cent

The alveolar air=4.66 liters which is 50.9 per cent of the minute-volume

The respiratory quotient=1.2

Dec 11, 1911, Sam B was more cyanotic than at the time the previous specimen was taken. His diet was also more liberal.

Time of collection=11 minutes

Rate of respiration=19.1 per min

Minute-volume=8.53 liters

Zuntz specimen  $\text{CO}_2$ =3.84 per cent or 0.327 L per minute,  $\text{O}_2$ =15.94 per cent

Alveolar air  $\text{CO}_2$ =9.77 per cent,  $\text{O}_2$ =10.73 per cent

Alveolar air=3.35 liters or 39.2 per cent of the minute-volume

Respiratory quotient=0.7

Another Zuntz specimen taken the same day

Time of collection=10 minutes

Average rate of respiration=27 per min

Minute-volume=8.73 liters

$\text{CO}_2$ =3.94 per cent or 0.343 liters per min

$\text{O}_2$ =16.9 per cent or 0.375 liters absorbed per min

Alveolar air=3.52 liters or 40.3 per cent of minute volume

Resp quotient=0.9

Dec 15, 1911 Cyanosis very pronounced

Time of collection=12 min

Minute volume=6.566 liters

Rate of respiration=27 per min

- Zuntz specimen  $\text{CO}_2$ =5.21 per cent per min = 0.342 liters,  $\text{O}_2$ =13.495 per cent or absorbed per min.=0.541 L

Alveolar air  $\text{CO}_2$ =9.59 per cent,  $\text{O}_2$ =10.09 per cent

The alveolar air=3.567 liters or 54 per cent of minute volume

Resp quotient=0.64

Compare the results with the same apparatus in my own respiration and we find that my alveolar air varied from 64 to 82 per cent of the minute-volume. When my respiratory rate was 10 per minute the alveolar air constituted from 64 to 77 per cent of the tidal air. Whereas, Sam B's alveolar air constituted only 50.9 per cent of the tidal air when he was breathing twelve times per minute and had a minute-volume of 9.16 liters.

It is obvious that if the minute-volume remains the same a slower rate of respiration will give a larger percentage of alveolar air in the minute-volume than when the rate of respiration is increased.

On Dec 15, 1911, a Zuntz specimen was taken from me with the following results

Time of collection=12 min

Rate per minute=10

Minute-volume=8.16 liters

This specimen contained  $\text{CO}_2$ =3.28 per cent,  $\text{O}_2$ =17.27 per cent

The alveolar air taken at the same time contained  $\text{CO}_2$ =5.05 per cent,  $\text{O}_2$ =14.9 per cent

Respiratory quotient=0.85

The alveolar air, therefore, equalled 64.8 per cent of the tidal air

From C F H—Another specimen Dec 19, 1911

Time of collection=11 min

Rate of resp per min=10

Minute volume=8.081 liters

This specimen contained  $\text{CO}_2$ =3.78 per cent,  $\text{O}_2$ =16.225

The alveolar air contained  $\text{CO}_2$ =4.86 per cent,  $\text{O}_2$ =15.24 per cent

Respiratory quotient=0.75

The alveolar air constituted 77.7 per cent of the minute volume

At a later date the experiment was tried of breathing as nearly fifteen times per minute as I could. The alveolar air at this time, in July, 1912, a warm day, contained 4.5 per cent  $\text{CO}_2$ .

The following are the results from three Zuntz specimens C F H

1 Time of collection=12 min, minute-volume=8.13 L, R rate=15.1 per minute,  $\text{CO}_2$ =2.7 per cent, Alveolar air=60 per cent,  $\text{CO}_2$  per minute, 222 cc

2 Time of collection=8 min, Minute volume=9.14 L, R rate=16 per min,  $\text{CO}_2$ =2.7 per cent, Alveolar air=59.9 per cent,  $\text{CO}_2$  per minute = 246 cc

3 Time of collection=7 min, Minute volume=9.76 L, R rate=16.3 per min,  $\text{CO}_2$ =2.4 per cent, Alveolar air=53.3 per cent,  $\text{CO}_2$  per min=234 cc

From these results it seems quite clear that the dead space in emphysema must be increased. There must be a considerable expansion of the lung between the alveoli and the large bronchi, otherwise I can see no explanation for the fact that in emphysema the alveolar air (which in this patient was so rich in  $\text{CO}_2$ ) should constitute such a small percentage of the tidal air when the rate of respiration and the minute-volume are normal or what conform to comfortable respiration and ventilation in a normal person.

In the case of Sam B the alveolar air was rich in  $\text{CO}_2$  and poor in oxygen. So the question naturally arose as to whether the cyanosis was due to an excess of  $\text{CO}_2$  or diminution in oxygen.

It was formerly shown that a great increase in the partial pressure of oxygen did not modify the cyanosis nor the rate or apparent minute-volume. An oxygen tank was connected with a rubber bag which communicated with the Zuntz apparatus. In this manner the patient was enabled to breathe an atmosphere of pure oxygen. A sample was taken from the tank which yielded 93 per cent of oxygen on analysis.

Sam B had a respiratory rate of 22 per minute on this day (April 19, 1911), and maintained the same rate during the time the Zuntz specimen was collected. The time of collection was eight minutes. The minute-volume 8.431 liters. The sample contained 2.5 per cent of  $\text{CO}_2$ . Another specimen was collected during 10 minutes and 40 seconds. The minute-volume was 9.510 liters. The respiratory rate varied between 20 and 25 per minute. The sample contained

$\text{CO}_2=2.9$  per cent,  $\text{O}_2=91.2$  per cent

In spite of the fact his alveoli were constantly filled with oxygen the cyanosis remained the same. We then took a Zuntz specimen from Sam B when he was breathing atmospheric air with the following results:

Time of collection=8 min

Minute-volume=7.895 liters

Resp. rate=22 per min

Zuntz specimen  $\text{CO}_2=2.21$  per cent,  $\text{O}_2=19.5$  per cent

Alveolar air  $\text{CO}_2=8.05$  per cent,  $\text{O}_2=12.3$  per cent

Sam B was then instructed to breathe twelve times, as deeply and rapidly as he could. At the end of this forced breathing the alveolar air contained

$\text{CO}_2=6.79$  per cent,  $\text{O}_2=15.71$  per cent

During March, 1912, the opportunity was given to prove the interpretation given Sam B's cyanosis and emphysema, in a patient who entered the hospital with pronounced pulmonary emphysema, air hunger and cyanosis. The cyanosis was not nearly so intense as in the case of Sam B, but the lungs extended downward to the seventh, ninth and eleventh ribs, respectively, in the nipple, axillary and scapular lines. Furthermore, the central tendon of the diaphragm occupied a low position as evidenced by the downward displacement of the liver and the strong approximation of the hypochondria toward the median line during inspiration. Although the patient breathed laboriously, the respiratory rate was 15 per minute and the same rate was maintained while breathing through the Zuntz

valves With the first trial, breathing was more laborious than when the apparatus was not used, consequently the minute-volume was large and a large amount of  $\text{CO}_2$  was given off

First experiment on A S March 29, 1912

Time of collection=15 min

Resp rate per min=14

Minute-volume=10 15 liters

The Zuntz specimen contained  $\text{CO}_2$ =2 37 per cent,  $\text{O}_2$ =18 1 per cent

Alveolar air  $\text{CO}_2$ =7 2 per cent,  $\text{O}_2$ =14 3 per cent

Respiratory quotient=0 79

$\text{CO}_2$  per min=0 241 liters

Alveolar air=3 341 liters or 31 8 per cent of the minute-volume

After further trials A S learned to breathe through the apparatus with less effort The following test is a specimen taken when the minute volume was less, but the respiratory rate was the same, viz, 14 per minute

Time of collection=11 minutes

Resp rate=14

Minute-volume=8 059 liters

The Zuntz specimen contained  $\text{CO}_2$ =2 16 per cent,  $\text{O}_2$ =18 7 per cent

Alveolar air  $\text{CO}_2$ =7 44 per cent,  $\text{O}_2$ =12 44 per cent

Total  $\text{CO}_2$  per min=0 174 liters

Resp quotient=0 9

Alveolar air=2 339 liters or 29 7 per cent of the minute volume

A few days later A S was much more comfortable There was no cyanosis, but the respiratory rate remained the same as when the patient was cyanotic The lower borders of the lungs were still at the seventh, ninth and eleventh ribs but the central tendon of the diaphragm was evidently not so low Although the costal angle did not widen during inspiration there was not the strong approximation of the hypochondria as formerly, when cyanosis was present and the bronchial wheezing was more pronounced

Third specimen from A S, April 1, 1912

While the Zuntz specimen was collected the patient breathed easily at the rate of 15 per minute

Time of collection=13 minutes

Resp rate=15 per min

Minute volume=6 380 liters

Zuntz specimen contained  $\text{CO}_2$ =2 7 per cent,  $\text{O}_2$ =18 4 per cent

Alveolar air  $\text{CO}_2$ =5 3 per cent,  $\text{O}_2$ =15 5 per cent

Resp quotient=1 0 per cent

$\text{CO}_2$  in minute volume=0 172 liters

Alveolar air=3 250 liters or 50 9 per cent of the minute volume

When the third specimen was taken it must be observed that the respiratory rate was 15 as compared with 14 in the second specimen, and although the minute-volume in the third specimen was 6 380 L, as compared with 8 059 L in the second specimen, the lung ventilation was much better, for the alveolar air constituted 50 9 per cent of the minute-volume in the third specimen, and only 29 7 per cent in the second specimen Moreover, at the time the third specimen was taken the patient had no cyanosis and the alveolar air contained 5 3 per cent of  $\text{CO}_2$  When the second specimen was taken, cyanosis was pronounced and the alveolar air contained 7 44 per cent  $\text{CO}_2$  With a lesser minute-volume and the same respiratory rate there was much better lung ventilation

The corollary from the experiment is that the respiratory rate and minute-volume (when studied apart from the  $\text{CO}_2$  content of the tidal and alveolar air) are no guides for estimating the real ventilation of the lung when bronchiolar volume is a factor under consideration

Another mode of reaction is exemplified in the following patient, Mrs L, who entered Lakeside Hospital in June, 1912. This patient was a small, thin woman who weighed 100 pounds. For two years she had had dyspnea and could do very little work on account of her respiratory limitations. The heart was not enlarged, there were no signs of any cardiovascular disease, i. e., disease of the heart, or aortic or pulmonary circulation. There were no evidences of any mediastinal disease. The lungs were emphysematous and were situated at the seventh, tenth and eleventh ribs, respectively in the nipple, axillary and scapular lines. During inspiration the lower end of the sternum was retracted and the epigastrium protruded. The costal angle was not enlarged during inspiration. The costal borders to the eighth ribs did not diverge during inspiration, but below the eighth ribs there was marked respiratory divergence of the costal borders, so the base of the thoracic cage had a marked increase in the transverse diameter during inspiration. Mrs L was not cyanotic but she complained of air hunger and had a respiratory rate of 26 during her stay of three weeks in the hospital. There was no pronounced cyanosis but at times there was a suggestion of cyanosis in the cheeks, but the fingers, ears, or tongue never revealed any pronounced cyanosis. This patient evidently retained her normal respiratory threshold and therefore breathed rapidly to compensate for poor alveolar ventilation. Consequently in this patient there were two factors which contributed to lowering the percentage of alveolar air in the minute-volume of respired air, viz., emphysema and a rapid respiratory rate.

Zuntz specimens taken from Mrs L gave the following results

Time of collection=9 minutes

Resp rate=25 11 per minute

Minute-volume=7 800 L

Sample of Zuntz specimen  $\text{CO}_2$ =1.48 per cent,  $\text{O}_2$ =19.3 per cent

Alveolar air  $\text{CO}_2$ =5.55 per cent,  $\text{O}_2$ =13.44 per cent

Respiratory quotient=0.8

Alveolar air=26.6 per cent of minute-volume

$\text{CO}_2$  per minute=115 cc

Another specimen showed the alveolar air to equal 29.4 per cent of the minute-volume

These three patients all present some signs which they have in common, and in other respects they differ greatly. All had increased pulmonary volume, and, indeed, so far as objective signs of pulmonary volume are concerned, they all had their lungs in the maximum inspiratory volume. All had the characteristic skodaic resonance and all had the prolonged expiratory phase.

Sam B had much more evidence of bronchitis than A S or Mrs L. Sam B was always cyanotic. A S had cyanosis only during his first week in the hospital. Mrs L never had pronounced cyanosis. Sam B never suffered air hunger. A S had air hunger only during the period of cyanosis, and Mrs L was never free from air hunger.

If we compare the results in Mrs L with the results in A S there is at first glance apparently a marked inconsistency in the results obtained in the two patients.

The second specimen from A S gave a minute-volume of 8 059 liters His alveolar air contained 7 44 per cent of  $\text{CO}_2$

Mrs L showed in repeated tests a minute-volume a little less than eight liters Her alveolar air always contained between 5 5 per cent and 6 per cent of  $\text{CO}_2$  Her alveolar air ranged between 26 per cent and 30 per cent of the minute-volume But A S was cyanotic at the test referred to, and Mrs L was never cyanotic There was this difference, however—A S had a respiratory rate of only fifteen per minute, whereas Mrs L had a respiratory rate which was constantly from 23 to 26 per minute That the lung ventilation was better in Mrs L must be granted because she was not cyanotic and her alveolar air had a  $\text{CO}_2$  content of from 5 5 per cent to 6 per cent The fact that her alveolar air constantly composed only 26 to 30 per cent of the minute-volume (as in A S) must then be due to the increased respiratory rate

I have compared my own lung ventilation with the ventilation of emphysematous lungs when I employed the same respiratory rate and minute-volume which the emphysematous patients had, and found my alveolar air under these conditions represented 60 per cent of the alveolar air as against 30 per cent in the emphysematous patients But this comparative test of respiratory rate and minute-volume and alveolar air was a comparison between a healthy person and emphysematous patients who were cyanotic I therefore wished to compare my lung ventilation with that of an emphysematous patient who was not cyanotic

I then took a Zuntz specimen from myself when I breathed twenty-five times per minute and endeavored to breathe so that the minute-volume would be the same as in Mrs L This was accomplished by setting up a mirror before the dial of the spirometer so that the excursion of the indicator could be seen and thus, at will, the amount of each respiratory excursion could be made to conform to the desired minute-volume An assistant beat time so that the number of respirations could be timed for exactly 25 respirations per minute Thus the minute-volume respiration of Mrs L was accurately imitated in my own breathing While this artificial respiratory rate and minute-volume were maintained it was desirable also to know what the  $\text{CO}_2$  content of the alveolar air might be For this purpose the mouth-piece of the Zuntz apparatus was fitted with a lateral opening through which a sample of alveolar air could be procured at the end of the experiment It was necessary to know the oxygen and carbonic acid content, not only for estimating the proportion of alveolar air to the minute-volume of air, but also to see if the percentage of carbonic acid in the alveolar air conformed to the sense of air hunger which prevailed during the time the Zuntz specimen was being taken The alveolar air was taken on the end of the last expiration of the seven minutes during which the Zuntz specimen was taken

Time of collection=7 min  
 Resp rate=25 per min  
 Min -vol=7 400 L  
 Resp quot=0 66  
 Per cent of alv air of the min vol=39 7 per cent  
 Zuntz specimen  $\text{CO}_2$ =2 6 per cent,  $\text{O}_2$ =17 3 per cent  
 Alveolar air  $\text{CO}_2$ =6 7 per cent,  $\text{O}_2$ =13 2 per cent

Another trial was made during which the sense of air hunger was not so severe as during the above test, but the sense of air hunger was pronounced

Time of collection=8 min  
 Resp rate=25 per min  
 Min -vol=7 570 L  
 Resp quot=0 65  
 Per cent of alv air of the min -vol=44 9  
 Zuntz specimen  $\text{CO}_2$ =2 8 per cent,  $\text{O}_2$ =17 0 per cent  
 Alveolar air  $\text{CO}_2$ =6 27 per cent,  $\text{O}_2$ =13 73 per cent

When the results are compared with those of Mrs L it will be noted that the alveolar air represented a larger portion of the minute-volume than in the case of Mrs L and although my sense of air hunger was pronounced, as was also quite evident in Mrs L, my alveolar air at the end of the experiment contained 6 7 per cent and 6 2 per cent of  $\text{CO}_2$ . Whereas Mrs L's alveolar air contained only 5 5 per cent. This seemed too low to be consistent with her sense of air hunger, the degree of emphysema, and also the suggestion of cyanosis in her face, which amounted to a slightly dusky hue, although as has been stated there never was pronounced cyanosis of the fingers, ears or tongue. The estimates of Mrs L's alveolar air compared with her minute-volume of air always proved the lung ventilation to be poor. As has been shown, when I employed the same respiratory rate and minute-volume as Mrs L., my alveolar air represented 10 per cent. more of the minute-volume than was the case with Mrs L, although the percentage of  $\text{CO}_2$  in my alveolar air was higher than Mrs L. In spite of this comparison it never seemed to me that we quite got the alveolar air of Mrs L. The degree of emphysema and air hunger always seemed inconsistent with such a moderate elevation of partial pressure in the  $\text{CO}_2$  of her alveolar air. From our former experiences with emphysema, too, it seemed reasonable to expect a better tolerance of such an elevation of  $\text{CO}_2$  content of the alveolar air, in a patient who had emphysema continuously for two years. I mean by this that the sense of air hunger was disproportionately great for the  $\text{CO}_2$  content of the alveolar air as estimated from a specimen of air procured at the end of a strong, quick, voluntary expiration.

Mrs L was a frail woman with a thin thorax which could be easily compressed. As we thought the real alveolar air may be better procured by compressing the thorax at the same time a voluntary expiratory effort was made, the following experiments were then made

A Zuntz specimen was taken for 11 minutes  
 The minute-volume was 7 522 liters  
 Respiratory rate  $22\frac{1}{2}$  per min



Zuntz specimen  $\text{CO}_2=19$  per cent,  $\text{O}_2=19.0$  per cent

The alveolar air was then taken at the end of a voluntary expiration. The first specimen contained 57 per cent of  $\text{CO}_2$ . The second specimen 61 per cent of  $\text{CO}_2$ .

The patient breathed through the tube used in procuring alveolar air and then as she was instructed to blow, her nose was closed by one assistant, another seated behind the patient forcibly compressed the thorax as the forced expiration was made, and immediately the specimen of air was taken. This was all done so quickly that the time factor could not be responsible for a high  $\text{CO}_2$  content. The specimen was procured as promptly as at other times when there was no compression of the thorax employed. The alveolar air procured in this manner had a  $\text{CO}_2$  content of 67 per cent which seemed quite consistent with the whole clinical picture.

The patient, A. S., had a  $\text{CO}_2$  content of 74 per cent in his alveolar air when he was cyanotic and 53 per cent a few days later when he was not cyanotic.

If the percentage of alveolar air is estimated on the basis of 67 per cent  $\text{CO}_2$ , then the alveolar air will constitute 28.3 per cent of the minute-volume. If the estimate is made on the basis of 61 per cent, the alveolar air constitutes 31.1 per cent of the minute-volume.

This method of compressing the thorax was employed in the case of Sam B., whose alveolar air at the time contained 83 per cent of  $\text{CO}_2$ , and the results obtained were the same as when no compression was employed. His thorax was unyielding and the trunk muscles were powerful.

The same results as in Sam B. were obtained in two healthy well-muscled men. It seems probable that in the case of Mrs. L. 67 per cent more nearly represents the  $\text{CO}_2$  content of her alveolar air than 53 per cent, or 61 per cent, which were the minimum and maximum percentages obtained in a dozen analyses, made at different times.

This method of estimating the lung ventilation proved to be of service in studying the case of a man 71 years old who gave a history of air hunger which existed two months before entering Lakeside Hospital.

This patient, L. S., was a powerful man with a large and very resistant thoracic cage. The only complaint the patient had was constant air hunger and frequent attacks of hyperpnea which awakened him at night. There was no cyanosis nor evidences of any cardiovascular disease. There was marked retraction of the costal borders and narrowing of the costal angle during inspiration. The lungs were voluminous. The finger nails were ridged and he gave a very clear history of gout which had been diagnosed by several physicians.

At the base of the right thorax in the axillary line there was movable dulness which was not pronounced, but gave rise to the suspicion of fluid in the right pleural cavity. Although the lungs were voluminous (at the ninth rib in the axillary lines), and the respiratory movements of the hypochondria betrayed a low position of the central tendon of the diaphragm, yet there were no signs of bronchitis.

The real question in this case was to account for the low position of the central tendon of the diaphragm. The  $\text{CO}_2$  of his alveolar air was first determined from specimens procured at the end of a forced expiration and found to be 37 per cent, 38 per cent and 39 per cent in three specimens. Compression was then employed at the end of the expiration and the  $\text{CO}_2$  content was 35 per cent, 37 per cent and 42 per cent in three specimens.

A Zuntz specimen was then taken for nine minutes.

The minute vol = 7.405 L.

The rate of respiration = 16 per min.

The an sample  $\text{CO}_2=19$  per cent,  $\text{O}_2=19.0$  per cent

Alveolar air taken directly after the Zuntz specimen was finished gave a  $\text{CO}_2$  content of 3.2 per cent and 3.3 per cent in two specimens

The alveolar air equalled 58 per cent of the minute-volume therefore the low position of the diaphragm could not be due to emphysema of bronchial origin

A skiagram of the thorax was then made and a tumor in the mediastinum directly behind the heart was clearly definable which displaced the central tendon downward. An exploratory needle was then inserted and a thin layer of fluid was located at the base of the right thorax. The fluid was not bloody, but contained a few red cells and many mononuclear cells. The patient left the hospital, but the skiagram justified the diagnosis of a mediastinal tumor which simulated bronchial emphysema by its displacement of the central tendon of the diaphragm. Had not the estimates of the minute-volume and alveolar air been made we would have overlooked the real disease and regarded the whole difficulty as bronchial emphysema with nocturnal asthma.

In the cases of Sam B. and Mrs. L. atropin and epinephrin (adrenalin) were given subcutaneously to see if the percentage of  $\text{CO}_2$  in their alveolar air could be modified. One thirty-fifth grain of atropin sulphate and 20 minims of 1:1,000 epinephrin were given in each case. The  $\text{CO}_2$  content of the alveolar air remained the same in both patients before and after the use of both atropin and epinephrin.

#### CONCLUSIONS

The essential result of these observations of pulmonary emphysema is the direct evidence that in emphysema the patient suffers from an impaired alveolar ventilation of the lung and not from an impairment of the lung as the organ of external respiration. Furthermore, the evidence seems very conclusive that the alveolar air constitutes a very diminished part of the minute-volume of air. So the minute-volume in any given case of emphysema is not a measure of alveolar ventilation. This diminution of the proportion of alveolar air must be due to an increase of the dead space. How can we account for an increase of the dead space in pulmonary emphysema? Can the increase of the dead space be explained best by bronchiolar spasm, bronchiolar atony, or swelling of the bronchial mucosa? Bronchiolar atony, that is, an elongation and broadening of the bronchioles, seems the most consistent with an increase of the dead space. Bronchiolar spasm or swelling of the bronchial mucosa could give an increase of the dead space only by an inspiratory enlargement of that portion of the air passage which lies between the alveoli and the larynx.<sup>4</sup>

I hope in the near future to present the evidence from some completed animal experiments which will throw light on this question.

In conclusion I wish to thank Dr. Chauncy Wycoff, former resident of Lakeside Hospital, and Dr. L. H. Taylor, resident physician at Lakeside Hospital, for their valuable assistance in this work.

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<sup>4</sup> Douglas and Haldane suggest the neuromuscular activity of the bronchiolar system as a source for enlarging and diminishing the dead space under physiological conditions. Jour. Physiol., Oct. 22, 1912, No. 4.

## A FURTHER STUDY OF THE VENTILATION OF SLEEPING CARS (THE STEEL CAR)

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Two years ago I presented before the American Public Health Association the results of a study of the ventilation of sleeping cars<sup>1</sup> An attempt was made to determine the amount of fresh air which enters the running car under various conditions of operation, the places of entrance of the air, its distribution, and the general direction of its currents Two plans of ventilating were considered in that study, which were called "natural ventilation" and "ventilation by exhaustion"

The essential architectural features of the standard American railway car are, as they concern the question under discussion, that it contains one long room with end doors opening to vestibules, and side windows, and was originally intended to receive its air supply through a row of small windows set in near the roof line on either side and called deck-sashes Part of the cars investigated in the study referred to were ventilated in this way, as are still the vast majority of the railway cars in this country Since natural forces alone are depended on to induce air interchange, this plan was referred to as "natural ventilation"

To the majority of the cars investigated there had been applied a device<sup>2</sup> intended to remove air through certain of these upper windows, or deck-sashes, by a suction effect dependent on train motion, all other deck-sashes remaining closed This plan was called "ventilation by exhaustion" It would tend to reverse the fresh air currents from a downward to an upward direction, instead of air being admitted at the top by natural forces through openings provided for that purpose and allowed to find its own way out, it would be removed at the top by artificial devices and left to find its own way in That the exhaust apparatus actually did what it was intended to do was easily determined by means of the anemometer It was found that each of these exhaust ventilators would remove about 15,000 cubic feet of air each hour at a forty-mile

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1 Crowder A Study of the Ventilation of Sleeping Cars, *THE ARCHIVES INT MED*, 1911, vii, 85

2 The Garland Ventilator This is described in the *Railway Age*, 1906, xli, 847, and in the *Railway Age Gazette*, 1910, l, 1757

train speed. Six to eight of them were applied to each car. The problem then was to determine the manner of entrance of the air, the general course of its currents, and the efficiency of the device in maintaining a fresh air supply to the breathing zone for the passengers and to the occupied berth, and to compare the results obtained by the two methods of ventilation. This was done by determining the respiratory contamination of the air of the car as represented by the proportion of carbon dioxide in the air. It is well known that from such determinations air supplies can be computed<sup>3</sup> with considerable accuracy.

The results of a large number of observations showed that by the application of this exhaust device the active ventilation of the body and

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3 The problem is simple. The air supply is inversely as the respiratory contamination. It may be computed from the following equation

$$A = \frac{vp}{x - N}$$

where  $v$  = the CO<sub>2</sub> produced by one person (cu ft per hour),  
 $p$  = the number of people in the car,  
 $x$  = the proportion of CO<sub>2</sub> found in the air of the car,  
 $N$  = the proportion of CO<sub>2</sub> in the outside air,  
 and  $A$  = the air supply to the car (cu ft per hour)

It is seen that  $vp$  is the CO<sub>2</sub> produced by the occupants and  $x - N$  is the respiratory contamination. We may substitute known values for the letters  $v$  and  $N$  in the above equation. The amount of CO<sub>2</sub> produced by one person will average very close to 0.6 cu ft per hour, and the average proportion of CO<sub>2</sub> in the air surrounding trains has been found to be very close to 0.0004, or 4 parts in 10,000. Making the substitution the equation becomes

$$A = \frac{0.6 p}{x - 0.0004}$$

Completing the computation of air supply for various assumed proportions of CO<sub>2</sub>, the results would be, when the space is occupied by one person only, i. e., when  $p$  is the unit 1, as follows

CO <sub>2</sub> = 0.0020 (resp. contam. = 0.0016),	hourly air supply = 375 cu ft
CO <sub>2</sub> = 0.0016 (resp. contam. = 0.0012),	hourly air supply = 500 cu ft
CO <sub>2</sub> = 0.0012 (resp. contam. = 0.0008),	hourly air supply = 750 cu ft
CO <sub>2</sub> = 0.0010 (resp. contam. = 0.0006),	hourly air supply = 1,000 cu ft
CO <sub>2</sub> = 0.0009 (resp. contam. = 0.0005),	hourly air supply = 1,200 cu ft
CO <sub>2</sub> = 0.0008 (resp. contam. = 0.0004),	hourly air supply = 1,500 cu ft
CO <sub>2</sub> = 0.0007 (resp. contam. = 0.0003),	hourly air supply = 2,000 cu ft
CO <sub>2</sub> = 0.0006 (resp. contam. = 0.0002),	hourly air supply = 3,000 cu ft
CO <sub>2</sub> = 0.0005 (resp. contam. = 0.0001),	hourly air supply = 6,000 cu ft

These same figures apply to a room with any number of occupants provided we add "per person" after "hourly air supply." In order for the air to maintain a constant respiratory contamination the volume supplied must be multiplied as often as we multiply the occupants—the air-supply must maintain a constant ratio to the CO<sub>2</sub> produced. Each person will contaminate 1,000 cu ft of air per hour to the extent of 6 parts of CO<sub>2</sub> in 10,000 of air (and the total CO<sub>2</sub> will be 10 parts in 10,000). One person will need simply the 1,000 cu ft per hour if the contamination is to be held at this level, fifty will need 1,000 cu ft each, or 50,000 cu ft. The estimation of air supply to a car must be based on the total amount of CO<sub>2</sub> produced by all of its occupants.

berths of a sleeping car is considerably increased over and above what may be expected from the natural forces of the wind through the open deck-sashes, and that the flow of fresh air into the car is more regular and better distributed. The many crevices about doors and windows act as intakes and the trend of the currents is of course upward. The respiratory contamination of the air of the breathing zone and of the occupied berth remains almost constantly low. Carbon dioxide reaches a proportion of ten parts in 10,000 of air with relative rarity, and the computed fresh air supply averages about 2,000 cubic feet per hour for each berth and about 40,000 cubic feet per hour for the car.

With the adoption of this exhaust system of ventilation as a standard of construction the deck-sashes cease to perform any important function. Indeed, they may become a direct hindrance to the most efficient operation of the device. They are of necessity, from their location and the method of their operation, loose fitting windows which furnish large crevices for air leakage. Since these crevices are located very near the outlets of the exhaust ventilators, the air entering through them is liable to be drawn directly out again and to play no part in effecting air renewal of the breathing zone. Furthermore, it tends to prevent air being drawn upward from the window crevices located below and the effective renewal of the air of the lower levels. That such short-circuiting does take place was shown in the study referred to, whereas by actual measure, some 80,000 cubic feet of air leaves the car each hour through the exhaust ventilator openings, there is only about 40,000, as computed from  $\text{CO}_2$  determinations, supplied to the breathing zone. The difference between the aeration of the breathing zone and the total air supply is not so great, however, as these figures would seem to indicate, since it is well known that  $\text{CO}_2$  determinations generally give an air supply which is under rather than over the actual. Furthermore, the estimate of total air outflow is here based on a constant forty-mile speed, whereas the estimates from  $\text{CO}_2$  include all rates of running as well as short stops.

The study from which the foregoing is drawn was made on the standard Pullman sleeping car of wooden construction. The exhaust ventilator considered was applied to cars which had been previously in service and had been originally ventilated by the natural or deck-sash method. Since the completion of that study the all-steel sleeping car has come into extensive use. These cars are all equipped with exhaust ventilators in the building, and for the reasons stated above the deck-sashes are omitted, or, if not entirely omitted, they are reduced from twenty-four to four, and these four are very small. Only electricity is used for lighting, this avoids the necessity of making openings through the roof to carry away the combustion gases of burning lights. The upper portion of the car is almost entirely free from natural openings.

It is therefore readily seen that whatever air enters these cars must come from crevices about windows and doors located low down. From this it would naturally follow that the lower levels of the car receive a larger air supply than with the older type of construction. It is not considered a matter of great hygienic importance whether they do or do not, no increase in the air supply is demanded on hygienic grounds, but in order to have some adequate information as to what actually does take place and to be able to make accurate comparisons, a series of thirty-six steel cars were investigated during the first two months of 1912.

The methods used in the investigation of these cars are the same as those previously employed. They are fully outlined in the original paper,<sup>1</sup> to which those interested are referred. Samples of the air to be examined were collected in glass-stoppered bottles, sealed, and were analyzed in the Petterson-Palmquist apparatus for the determination of carbon dioxide. Air was collected from the center aisle, in order to determine the respiratory contamination of the general air of the car, and from lower and upper berths in order to determine the respiratory contamination of the air within them. From these contaminations air supplies have been computed as has been previously explained.<sup>3</sup>

All the observations in the cars included in the present series were made during the night, after the passengers had retired. The time ranged from 11 00 p. m. to early morning. The outside temperature varied from 0 F. to 36 F., it was generally as low as 20 F. Samples were taken as nearly simultaneously as possible in the aisle and in from three to six berths, samples from the same places were repeated at approximately fifteen minute intervals for one or two hours. This was done in order to obtain general averages, which are more important and give much more dependable information of the condition of the air than single observations or short series. From the latter erroneous conclusions are very likely to be drawn. It must be recognized that in any running car the conditions are liable to rapid and relatively great variation. Minimum actual rates of air supply, hence degrees of respiratory contamination, alternate with maximum actual rates, and these minimums and maximums may lie a considerable distance apart. They represent temporary and local, not continuous and general, conditions. General averages are much more significant.

#### GENERAL RESULTS

In Table 1 are assembled the more important items concerning the general air of the cars examined. The air tests recorded in this table refer only to the samples collected from the car body, and not to those collected from the berths. The air supply as computed is expressed to

the nearest thousand in terms of cubic feet per car per hour. It is that volume which would keep the CO<sub>2</sub> at the average proportion found in the air of the car if the number of occupants did not change.

TABLE 1—DETERMINATIONS OF THE VENTILATION OF STEEL SLEEPING CARS  
EQUIPPED WITH EXHAUST VENTILATORS

Experiment	Name of Car	Temp F		No of People in Car	CO <sub>2</sub> per 10,000 of Air				Approx Hourly Air Supply
		Out	In		No of Tests	Average	Extremes		
							Min	Max	
1	Cresheim	12	52	16	6	5.50	4.5	6.0	64,000
2	Millard*	36	60	15	8	5.25	4.5	6.5	72,000
3	Brightwood*	10	56	15	7	6.00	5.0	7.0	45,000
4	Thurston	30	56	28	7	6.79	6.0	8.5	60,000
5	Sparks†	34	60	18	10	5.45	4.5	7.0	74,000
6	Cresheim*	20	58	19	11	5.82	5.0	7.5	70,000
7	Parkerton*	24	61	10	9	5.28	4.5	6.0	47,000
8	Bridgeport*	24	60	10	8	5.56	4.5	6.5	38,000
9	Millard‡	26	59	14	9	4.77	4.5	5.5	109,000
10	Lemay‡	26	60	15	9	4.72	4.5	5.0	125,000
11	Amsden	30	60	18	7	6.00	5.0	8.0	54,000
12	Walworth	30	63	17	7	5.71	5.0	8.0	59,000
13	Thurston	24	54	19	7	6.57	6.0	7.0	44,000
14	Moorfield	24	60	18	7	5.93	5.5	6.5	56,000
15	Bogero	20	58	12	7	5.21	4.5	5.5	59,000
16	Somena	20	58	16	7	5.50	5.0	6.0	64,000
17	Wawa	30	62	18	9	6.39	5.5	9.5	45,000
18	Nepperhan	24	63	18	7	5.79	5.0	7.0	60,000
19	Monterth	24	58	16	7	6.36	5.5	7.0	41,000
20	Ship Road	6	60	12	7	5.14	4.5	6.0	63,000
21	Hyndman	6	60	8	7	4.79	4.5	5.5	57,000
22	Thurston§	6	58	26	7	7.21	6.0	9.5	49,000
23	Roseton§	6	60	22	4	8.13	7.5	8.5	32,000
24	Colfax	16	60	16	6	5.92	5.0	8.0	50,000
25	Dorrance	16	60	17	5	5.40	5.0	5.5	72,000
26	Onchota	24	60	15	5	5.20	4.5	6.0	75,000
27	Canfield	24	60	21	5	7.10	6.0	8.0	41,000
28	Cariothers	0	58	15	6	5.83	5.0	6.5	49,000
29	Wawa	0	58	14	6	6.66	5.5	8.0	33,000
30	Elkland	8	56	20	5	6.30	5.5	7.5	52,000
31	Onchota	8	56	15	6	6.25	5.5	7.0	40,000
32	Middletown	8	68	12	3	5.33	5.0	5.5	54,000
33	Josslyn	20	62	15	5	5.30	5.0	5.5	69,000
34	Halleck	20	62	12	6	5.08	4.5	6.0	67,000
35	Millard	12	58	12	7	5.07	5.0	5.5	74,000
36	Henefer	12	60	10	7	4.93	4.5	6.0	65,000
	36 cars			162	246	5.78	4.5	9.5	54,600

\*Drop-sashes of end doors open 3 inches (see note 4)

†Drop-sash of rear door open 12 inches (see note 4)

‡Drop-sashes of end doors open 24 inches (see note 4)

§Train running directly with a strong wind

The observations from which Table 1 is compiled may be summarized as follows

Cars examined	36
Average number of occupants	16.2
Number of air samples analyzed	246
Average number of samples per car	6.86
Average carbon dioxide	5.78 10,000
Highest average CO <sub>2</sub> in any car	8.13 10,000
Lowest average CO <sub>2</sub> in any car	4.72 10,000
Highest CO <sub>2</sub> in any sample	9.5 10,000
Lowest CO <sub>2</sub> in any sample	4.5 10,000
Number samples showing CO <sub>2</sub> over 10 10,000	0 (0.00%)
Number samples showing CO <sub>2</sub> over 8 10,000	5 (2.03%)
Number samples showing CO <sub>2</sub> over 7 10,000	20 (8.13%)
Number samples showing CO <sub>2</sub> over 6 10,000	56 (22.76%)
Number samples showing CO <sub>2</sub> 6 or less 10,000	190 (77.24%)
Average hourly air supply per car, cu ft	54,600
Highest hourly air supply for any car, cu ft	125,000
Highest excepting Nos 9 and 10, <sup>4</sup> cu ft	75,000
Average excepting Nos 9 and 10, <sup>4</sup> cu ft	53,000
Lowest hourly air supply for any car, cu ft	32,000
Number of cars showing less than 40,000 cu ft per hour, 3	(8.33%)

The average air supply to the breathing zone of the steel sleeping car, as computed from the average proportion of CO<sub>2</sub> and the average number of occupants in the thirty-six cars examined, is found to be approximately 54,600 cubic feet per hour, as above stated, or, in those cars kept entirely closed, even to drop-sashes in the end doors,<sup>4</sup> 53,000 cubic feet per hour

4 The end doors of the car are fitted with small sliding windows, which may be lowered from the top and held at any level by a catch. These windows are commonly referred to as "drop-sashes." In regular service it is customary to maintain a variable opening of these windows in order to facilitate the entrance of fresh air from the vestibule. During the first ten experiments they were left alone as found, in all later experiments they were purposely kept closed while observations were being made.

An examination of Table 1 will show that only twice, namely, in Experiments 9 and 10, was the air supply markedly affected by these open drop-sashes, and in these cars the sashes were opened widely. These two cars were on the same train and air samples from the two were collected at approximately the same time. The air supply in these two instances is so greatly increased as to show a considerably higher average air supply and lower CO<sub>2</sub> for the small group of eight cars which had some opening of the drop-sashes, than for the others in which there was no opening at all. The averages for the eight cars are CO<sub>2</sub>, 5.34, occupants, 14.7, equivalent air supply, 65,900 cu ft per hour. The averages for all other cars, which had no openings in the end doors, are CO<sub>2</sub>, 5.90, occupants, 16.8, equivalent air supply, 53,000 cu ft per hour. Leaving out of consideration only Nos 9 and 10 the other thirty-four cars show the following averages CO<sub>2</sub>, 5.85, occupants 16.3, air supply 53,000 cu ft per hour. It is seen that the final results are affected only slightly by including in the general averages the findings in these two cars.

The general averages as above noted and as used throughout are found by adding together all single observations and dividing by the total number, and not by adding the car averages. The two methods will often give slightly different results, but the difference has never been found great enough to make material changes.



TABLE 2—DETERMINATIONS OF THE VENTILATION OF THE LOWER BERTHS OF STEEL SLEEPING CARS  
EQUIPPED WITH EXHAUST VENTILATORS

Name of Car	Temp F		No of People in Car	Aisle			Lower Berths								Approx Hourly Air Supply per Berth
	Out	In		Average CO. per 10,000	Extremes		No Ex- hausted	Total No of Tests	Average CO. per 10,000	Extremes		Tests Over 12 10,000	Tests Over 10 10,000		
					Min	Max				Min	Max				
Cresheim	12	52	16	5 50	4 5	6 0	4	24	5 73	4 5	7 0	0	0	3470	
Millard*	36	60	15	5 25	4 5	6 5	4	32	6 64	4 5	10 0	0	0	2270	
Brightwood*	10	56	15	6 00	5 0	7 0	4	28	6 66	5 0	9 0	0	0	2250	
Thurston	30	56	28	6 79	6 0	8 5	3	21	7 12	5 5	10 5	0	1	1920	
Sparks†	34	60	18	5 45	4 5	7 0	3	30	6 18	4 5	9 5	0	0	2750	
Cresheim*	20	58	19	5 82	5 0	7 5	4	44	6 69	5 0	9 5	0	0	2230	
Parkerton*	24	61	10	5 28	4 5	6 0	3	27	6 07	4 5	8 0	0	0	2900	
Bridgeport*	24	60	10	5 56	4 5	6 5	3	22	7 05	5 0	9 0	0	0	1970	
Millard‡	26	59	14	4 77	4 5	5 5	3	27	6 06	5 0	10 0	0	0	2910	
Lemay‡	26	60	15	4 72	4 5	5 5	2	18	6 06	5 0	7 5	0	0	2910	
Amsden	30	60	18	6 00	5 0	8 0	2	14	7 36	5 0	14 0	1	1	1790	
Walworth	30	63	17	5 71	5 0	8 0	3	21	7 64	4 5	14 0	1	4	1650	
Thurston	24	54	19	6 57	6 0	7 0	3	21	9 02	7 5	10 5	0	1	1200	
Moorfield	24	60	18	5 93	5 5	6 5	3	21	6 62	6 0	9 0	0	0	2290	
Bogero	20	58	12	5 21	4 5	5 5	4	28	6 41	5 0	8 0	0	0	2470	
Somena	20	58	16	5 50	5 0	6 0	2	14	6 64	5 5	8 0	0	0	2270	
Wawa	30	62	18	6 39	5 5	9 5	3	27	7 55	5 0	11 5	0	2	1690	
Nepperhan	24	63	18	5 79	5 0	7 0	3	21	6 09	5 0	7 5	0	0	2870	
Monterith	24	58	16	6 36	5 5	7 0	4	28	7 52	5 5	11 0	0	2	1700	
Ship Road	6	60	12	5 14	4 5	6 0	4	28	6 33	4 5	8 5	0	0	2570	
Hyndman	6	60	8	4 79	4 5	5 5	4	28	6 36	4 5	11 5	0	1	2540	
Thurston§	6	58	26	7 21	6 0	9 5	4	28	9 25	7 0	12 5	1	5	1140	
Roseton§	6	60	22	8 13	7 5	8 5	4	16	9 22	7 5	10 5	0	1	1150	
Colfax	16	60	16	5 92	5 0	8 0	4	24	7 01	5 5	10 0	0	0	1990	
Dorrance	16	60	17	5 40	5 0	5 5	4	20	5 85	5 5	6 5	0	0	3240	
Onchiota	24	60	15	5 20	4 5	6 0	4	20	5 55	4 5	6 5	0	0	3870	
Canfield	24	60	21	7 10	6 0	8 0	4	20	7 81	5 0	9 5	0	0	1570	
Carrothers	0	58	15	5 83	5 0	6 5	4	24	6 31	5 0	9 0	0	0	2600	
Wawa	0	58	14	6 66	5 5	8 0	4	24	6 93	5 0	9 0	0	0	2050	
Elkland	8	56	20	6 30	5 5	7 5	4	20	7 01	5 0	9 0	0	0	1990	
Onchiota	8	56	15	6 25	5 5	7 0	4	24	6 89	5 5	8 0	0	0	2080	
Hiddletown	8	68	12	5 33	5 0	5 5	4	12	6 50	5 5	7 5	0	0	2400	
Oslyn	20	62	15	5 30	5 0	5 5	4	20	5 91	5 0	6 5	0	0	3140	
Sallick	20	62	12	5 08	4 5	6 0	4	24	6 85	5 0	10 0	0	0	2110	
Millard	12	58	12	5 07	5 0	5 5	4	28	6 21	5 0	7 5	0	0	2720	
Henefer	12	60	10	4 93	4 5	6 0	4	28	5 91	5 0	8 5	0	0	3140	
36 cars			162	5 78	4 5	9 5	128	856	6 76	4 5	14 0	3	18	2170	

\*Drop-sashes of end doors open 3 inches (see Note 4)

†Drop sash of rear door open 12 inches (see Note 4)

‡Drop-sashes of end doors open 24 inches (see Note 4)

§Train running directly with a strong wind

This compares with 40,600 cubic feet per hour for the older type of car, equipped with the same ventilating device, but maintaining the deck-sash construction, and with 28,300 cubic feet per hour for cars having the ordinary deck-sash ventilation. The results in the steel car are also more uniform and more regular, as will be found by consulting the detailed results of the first group of experiments<sup>1</sup>. The complete comparative averages may be grouped as follows:

*A Wood Cars (with Deck-Sash Construction)*

1 Natural ventilation (deck-sash method)	
a Fully closed car	18 500 cu ft per hour
b With open deck-sashes	28,300 cu ft per hour
c With open deck-sashes and open end doors	40,700 cu ft per hour
2 Exhaust ventilation (the exhaust method)	
a Fully closed car	40,600 cu ft per hour
b With open doors	57,900 cu ft per hour

*B Steel Cars (Constructed Without Deck-Sashes)*

Exhaust ventilation	
a Fully closed car	53,000 cu ft per hour
b With open drop sashes in end doors <sup>2</sup>	65,900 cu ft per hour

Any or all of these figures might be changed by longer series of observations. For most of the groups it is believed a sufficient number have been made to insure the relative correctness of the results obtained.

### THE LOWER BERTH

In Table 2 are assembled the observations in lower berths and comparisons with the air of the aisle taken at the same time. It will be noted that the experiments recorded in this table are the same as those presented in Table 1, and that they cover all the cars investigated. The air supply per berth, as computed, is the number of cubic feet which must be supplied to one person each hour in order to maintain the  $\text{CO}_2$  at the average proportion found. The berths included in this list were each occupied by one adult.

The observations from which Table 2 is compiled may be summarized as follows:

Cars in which lower berths were examined	36
Number of lower berths examined	128
Average number of lower berths per car	3.56
Total number of air samples from lower berths	856
Average number of lower berth samples per car	23.78
Average number of samples per berth	6.53
Average $\text{CO}_2$ in air of car body	5.78 10,000
Average $\text{CO}_2$ in air of lower berths	6.76 10,000
Highest average $\text{CO}_2$ in lower berths of any car.	9.25 10,000
Lowest average $\text{CO}_2$ in lower berths of any car	5.55 10,000
Highest $\text{CO}_2$ in any lower berth sample	14 10,000
Lowest $\text{CO}_2$ in any lower berth sample	4.5 10,000

Number L B samples showing CO <sub>2</sub> over 12 10,000	3 ( 0 35%)
Number L B samples showing CO <sub>2</sub> over 10 10,000	18 ( 2 10%)
Number L B samples showing CO <sub>2</sub> over 8 10,000	137 (16 00%)
Number L B samples showing CO <sub>2</sub> over 7 10,000	238 (27 80%)
Number L B samples showing CO <sub>2</sub> over 6 10,000	476 (55 61%)
Number L B samples showing CO <sub>2</sub> 6 or less 10,000	380 (44 39%)
Number L B with higher CO <sub>2</sub> than aisle at same time	658 (76 87%)
Number L B with lower CO <sub>2</sub> than aisle at same time	68 ( 7 95%)
Number L B with CO <sub>2</sub> equal to aisle at same time	130 (15 19%)
Average hourly air supply per lower berth, cu ft	2170
Highest average hourly air supply to L B of any car, cu ft	3870
Lowest average hourly air supply to L B of any car, cu ft	1140
Number cars showing average of less than 1500 cu ft per L B per hour, 3'	(8 33%)

On the basis of 856 carbon dioxide determinations in the air of 126 lower berths in thirty-six steel sleeping cars equipped with exhaust ventilators, the average air supply per berth is found to be approximately 2170 cubic feet per hour. This compares with 2,030 cubic feet for the lower berths of the older type of cars equipped with the same ventilating device, and with 1,390 cubic feet in cars ventilated by the deck-sash method<sup>1</sup>

#### THE UPPER BERTH

Table 3 records the observations made in upper berths and comparisons with the air of the aisle taken at the same time. The items included are the same as those for the lower berths in the preceding table.

The results of examination of upper berths may be summarized as follows:

Cars in which upper berths were examined	21
Number of upper berths examined	30
Average number of upper berths per car	1 43
Total number of air samples from upper berths	207
Average number of upper berth samples per car	9 86
Average number of samples per berth	6 9
Average CO <sub>2</sub> in air of car body	5 86 10,000
Average CO <sub>2</sub> in air of upper berths	7 00 10,000
Highest average CO <sub>2</sub> in upper berths of any car	8 70 10,000
Lowest average CO <sub>2</sub> in upper berths of any car	5 44 10,000
Highest CO <sub>2</sub> in any upper berth sample	11 5 10,000
Lowest CO <sub>2</sub> in any upper berth sample	4 5 10,000

5 These figures may be converted into terms of air supply. For every proportion of CO<sub>2</sub> in the air there is an equivalent hourly air supply. When the CO<sub>2</sub> is 6 per 10,000 there is a dilution of the expired air which would be maintained by 3,000 cubic feet of fresh air per hour, when the proportion of CO<sub>2</sub> is less than 6 per 10,000 there must be more than 3,000 cubic feet per hour. The conversion gives the following results:

Lower berth tests showing 3000 or more cu ft per hour	44 39%
Lower berth tests showing 2000 or more cu ft per hour	72 20%
Lower berth tests showing 1500 or more cu ft per hour	84 00%
Lower berth tests showing 1000 or more cu ft per hour	97 90%
Lower berth tests showing 750 or more cu ft per hour	99 65%

6 These cars were Nos 13, 22 and 23. The last two were on the same train and samples were taken in them at approximately the same time. The train was running directly with a strong wind. Nos 13 and 22 are the same car, on different trips.

Number U B samples showing CO <sub>2</sub> over 12 10,000	0 ( 0 00%)
Number U B samples showing CO <sub>2</sub> over 10 10,000	5 ( 2 42%)
Number U B samples showing CO <sub>2</sub> over 8 10,000	34 (16 43%)
Number U B samples showing CO <sub>2</sub> over 7 10,000	83 (40 10%)
Number U B samples showing CO <sub>2</sub> over 6 10,000	139 (67 15%)
Number U B samples showing CO <sub>2</sub> 6 or less 10,000 <sup>7</sup>	68 (32 84%)
Number U B with higher CO <sub>2</sub> than aisle at same time	182 (87 92%)
Number U B with lower CO <sub>2</sub> than aisle at same time	13 ( 6 28%)
Number U B with CO <sub>2</sub> equal to aisle at same time	12 ( 5 80%)

Average hourly air supply per upper berth, cu ft 2000

Highest average hourly air supply for U B of any car, cu ft 4170

Lowest average hourly air supply for U B of any car, cu ft 1280

Number of cars showing average of less than 1,500 cu ft per U B per hour, 2 (9 52%)

TABLE 3 —DETERMINATIONS OF THE VENTILATION OF THE UPPER BERTHS OF STEEL SLEEPING CARS EQUIPPED WITH EXHAUST VENTILATORS

Experiment	Name of Car	Temp F		No of People in Car	Aisle			Upper Berths								Approx Hourly
		Out	In		Average CO <sub>2</sub> per 10,000	Extremes		No Ex- amined	Total No of Tests	Average CO <sub>2</sub> per 10,000	Extremes		Tests Over 12 10,000	Tests Over 10 10,000		
						Min	Max				Min	Max				
1	Cresheim	12	52	16	5 50	4 5	6 0	1	6	6 08	5 5	6 5	0	0	2	
2	Millard*	36	60	15	5 25	4 5	6 5	1	8	6 50	5 0	10 5	0	1	2	
3	Brightwood	10	56	15	6 00	5 0	7 0	1	7	6 79	6 0	8 5	0	0	2	
4	Thurston	30	56	28	6 79	6 0	8 5	1	7	8 36	7 0	11 0	0	1	1	
5	Sparks†	34	60	18	5 45	4 5	7 0	2	20	6 68	5 5	8 5	0	0	2	
6	Cresheim*	20	56	19	5 82	5 0	7 5	1	11	6 82	6 0	8 5	0	0	2	
10	Lemay‡	26	60	15	4 72	4 5	5 0	1	9	5 44	4 5	6 0	0	0	4	
11	Amsden	30	60	18	6 00	5 0	8 0	2	14	6 96	5 5	9 0	0	0	2	
12	Walworth	30	60	17	5 71	5 0	8 0	1	7	6 29	5 5	8 5	0	0	2	
13	Thurston	24	54	19	6 57	6 0	7 0	1	7	7 79	6 0	10 0	0	0	1	
14	Moorfield	24	60	18	5 93	5 5	6 5	1	7	7 43	6 0	8 5	0	0	1	
16	Somena	20	58	16	5 50	5 0	6 0	2	14	7 07	6 0	9 0	0	0	1	
17	Wawa	30	62	18	6 39	5 5	9 5	2	18	7 77	6 0	11 5	0	2	1	
18	Nepperhan	24	62	18	5 79	5 0	7 0	1	7	6 00	5 5	6 5	0	0	30	
22	Thurston§	6	58	26	7 21	6 0	9 5	1	7	7 79	6 5	9 5	0	0	1	
24	Colfax	16	60	16	5 92	5 0	8 0	2	12	7 42	6 0	9 5	0	0	1	
26	Onchiota	24	60	15	5 20	4 5	6 0	2	10	5 75	4 5	7 5	0	0	3	
27	Canfield	24	60	21	7 10	6 0	8 0	2	10	8 70	7 0	10 5	0	1	1	
30	Elkland	8	56	20	6 30	5 5	7 0	2	10	7 85	7 0	10 0	0	0	1	
33	Josslyn	20	62	15	5 30	5 0	5 5	2	10	6 45	6 0	8 0	0	0	2	
34	Halleck	20	62	12	5 08	4 5	6 0	1	6	6 25	5 5	6 5	0	0	28	
21 cars				17 8	5 86	4 5	9 5	30	207	7 00	4 5	11 5	0	5	20	

\*Drop-sashes of end doors open 3 inches (see Note 4)

†Drop-sash of rear door open 12 inches (see Note 4)

‡Drop-sashes of end doors open 24 inches (see Note 4)

§Train running directly with a strong wind

7 Converting these figures into terms of air supply, as in Note 5

Upper berth tests showing 3000 or more cu ft per hour, 32 84%

Upper berth tests showing 2000 or more cu ft per hour, 59 90%

Upper berth tests showing 1500 or more cu ft per hour, 83 57%

Upper berth tests showing 1000 or more cu ft per hour, 97 58%

Upper berth tests showing 750 or more cu ft per hour, 100 00%

On the basis of 207 carbon dioxide determinations in 30 upper berths of 21 steel sleeping cars equipped with exhaust ventilators, the average air supply per berth is found to be approximately 2,000 cubic feet per hour. This compares with 1,880 cubic feet for the upper berths of the older type of cars equipped with the same ventilating device, and with 1,270 cubic feet in cars ventilated by the deck-sash method.<sup>1</sup>

#### COMPARISON OF LOWER AND UPPER BERTHS IN THE SAME CAR

We are able to compare the ventilation of the lower and upper berths in all of the twenty-one cars in which upper berths were investigated. The comparison for each car is shown in Table 4.

It will be seen from this table that the ventilation of lowers and uppers is, on the average, much the same. It is relatively rare for the

TABLE 4—COMPARISON OF THE VENTILATION OF LOWER AND UPPER BERTHS IN STEEL SLEEPING CARS EQUIPPED WITH EXHAUST VENTILATORS

Experiment	Name of Car	CO <sub>2</sub> per 10,000 of Air					Equivalent Hourly Air Supply per Berth	
		Aisle	Lowers		Uppers		Lower	Upper
			No. of Tests	Aver. CO <sub>2</sub>	No. of Tests	Aver. CO <sub>2</sub>		
1	Cresheim	5.50	24	5.73	6	6.08	3470	2880
2	Millard*	5.25	32	6.64	8	6.50	2270	2400
3	Brightwood*	6.00	28	6.66	7	6.79	2250	2150
4	Thurston	6.79	21	7.12	7	8.36	1920	1360
5	Sparks†	5.45	30	6.18	20	6.68	2750	2240
6	Cresheim*	6.82	44	6.69	11	6.82	2230	2130
10	Lemay‡	4.72	18	6.06	9	5.44	2910	4170
11	Amsden	6.00	14	7.30	14	6.96	1790	2030
12	Walworth	5.71	21	7.64	7	6.29	1650	2620
13	Thurston	6.57	21	9.02	7	7.79	1200	1580
14	Moorfield	5.93	21	6.62	7	7.43	2290	1750
16	Somena	5.50	14	6.64	14	7.07	2270	1950
17	Wawa	6.39	27	7.55	18	7.77	1690	1590
18	Nepperhan	5.79	21	6.09	7	6.00	2870	3000
22	Thurston§	7.21	28	9.25	7	7.79	1140	1580
24	Colfax	5.92	24	7.01	12	7.42	1990	1760
26	Onchiota	5.20	20	5.55	10	5.75	3870	3430
27	Canfield	7.10	20	7.81	10	8.70	1570	1280
30	Elkland	6.30	20	7.01	10	7.85	1990	1560
33	Josslyn	5.30	20	5.91	10	6.45	3140	2450
34	Halleck	5.08	24	6.85	6	6.25	2110	2670
21 cars		5.86	492	6.93	207	7.00	2050	2000

Drop sashes of end doors open 3 inches (see Note 4)

†Drop sash of rear door open 12 inches (see Note 4)

‡Drop-sashes of end doors open 24 inches (see Note 4)

§Train running directly with a strong wind

average air supply of the two to fall far apart. If one is high the other is high, if one is low the other is low. The general averages show results which would indicate that the lower receives slightly more air than the upper, but the difference is almost trifling. In thirteen cars the lower received the greater air supply, in eight cars the upper received the greater supply. This runs in part counter to the findings of the previous study,<sup>1</sup> where in every car the lowers were found to receive a little more air than the uppers. In that series there were only five cars in which this comparison could be made.

The simultaneous averages of  $\text{CO}_2$  in the air of two to four lowers and in one or two uppers in the same car can be compared 148 times. The average proportion of  $\text{CO}_2$  in the air of the lowers was less than in the uppers 83 times (56.1 per cent), it was greater 58 times (39.2 per cent), and they were equal 7 times (4.7 per cent).

The proportion of  $\text{CO}_2$  in the air of the individual lower and upper berths in the same section, the samples being taken at approximately the same time, can be compared 185 times. The lower berth had less  $\text{CO}_2$  than the upper 96 times (51.9 per cent), it had more than the upper 62 times (33.5 per cent), and they were equal 27 times (14.6 per cent). The air supply is, of course, inversely as these proportions of  $\text{CO}_2$ , the lower had a greater air supply than the upper in 51.9 per cent, a less air supply than the upper in 33.5 per cent, and they were momentarily equal in 14.6 per cent of the cases.

The upper berth has no window opening into it. The edge of the berth is about on a level with the top of the window. There is a space of about one-half inch between the edge of the berth and the wall—a total open space of about 36 square inches. Through this wide crevice the upper berth receives much of its air supply, which must then pass inward and upward across the berth and its occupant toward the ventilator exits.

#### GENERAL COMPARISONS

We may here bring together the comparative results for the car body and the lower and upper berths in the three classes of cars. The general averages of  $\text{CO}_2$  and the computed air supplies are as follows:

##### *A Wood Cars (with Deck-Sash Construction)*

##### 1 Natural ventilation (Deck-Sash Method)

Body of car	$\text{CO}_2 = 7.32$ , air supply to car	$= 29,700$ cu ft per hour
Lower berth	$\text{CO}_2 = 8.32$ , air supply per berth	$= 1,390$ cu ft per hour
Upper berth	$\text{CO}_2 = 8.73$ , air supply per berth	$= 1,270$ cu ft per hour

##### 2 Exhaust ventilation (The Exhaust Method)

Body of car	$\text{CO}_2 = 6.33$ , air supply to car	$= 40,600$ cu ft per hour
Lower berth	$\text{CO}_2 = 6.96$ , air supply per berth	$= 2,030$ cu ft per hour
Upper berth	$\text{CO}_2 = 7.19$ , air supply per berth	$= 1,880$ cu ft per hour

B Steel Cars (Constructed without Deck-Sashes)

Exhaust ventilation

Body of car CO<sub>2</sub>=5.90, air supply to car =53,000 cu ft per hour  
Lower berth CO<sub>2</sub>=6.76, air supply per berth = 2,170 cu ft per hour  
Upper berth CO<sub>2</sub>=7.00, air supply per berth = 2,000 cu ft per hour

The comparisons made in the preceding summary will be made clearer by consulting Chart 1, in which the CO<sub>2</sub> and the equivalent hourly air supplies per person are grouped for the three classes of cars, showing their relations as established by a study of the air of the aisle, the lower berth, and the upper berth, respectively.

The preceding determinations of CO<sub>2</sub> and computations of air supply refer to the running car. When a train stops the active ventilation is much reduced and the CO<sub>2</sub> rises. It may finally reach a maximum of 20 volumes in 10,000, though it usually stops around 15. This rise in

CARBON DIOXID VOLUMES PER 10,000 OF THE AIR					KIND OF CAR METHOD OF VENTILATING	AIR SUPPLY CUBIC FEET PER PERSON PER HOUR				
9	8	7	6	5		4	0	1000	2000	3000
UPPER BERTH										
8 73						WOOD DECK SASH				1270
7 19						WOOD EXHAUST				1880
7 00						STEEL EXHAUST				2000
LOWER BERTH										
8 32						WOOD DECK SASH				1390
6 96						WOOD EXHAUST				2030
6 76						STEEL EXHAUST				2170
BODY OF CAR										
7 32						WOOD DECK SASH				1810
6 33						WOOD EXHAUST				2570
5 90						STEEL EXHAUST				3160

Chart 1—Comparative CO<sub>2</sub> and air supply of the berths and aisle in steel cars with exhaust ventilation, and in wood cars with exhaust and natural ventilation

the CO<sub>2</sub> is generally detected within a very short time—one or two minutes. On starting again the air supply is increased and the CO<sub>2</sub> falls rapidly. In working out the series of observations presented in this and

8 This figure applies to cars which have no opening of the drop sash in end doors (see Note 4), as the equivalent figures in the other group apply to cars with closed doors. The windows are closed in all cases.

9 Strictly considered there is no proper comparison of the aisles as set forth in this chart, because the number of passengers varied for the different classes of cars, and as this number varies the CO<sub>2</sub> and the volume of air per person will also vary in like ratio, with any given air supply to the car. The variation in the average number of passengers for the different classes was, however, so small as to make this direct comparison allowable. In the steel cars from which the figures are drawn the average was 16.3, in the wood cars with exhaust ventilation 15.7, and in the wood cars with natural ventilation 16.4, from which it is seen that the comparison is correct to within a small fraction. This is not greater than the unavoidable error of observation.

the previous study no attention was paid to stops lasting up to four or five minutes, samples taken after those of longer duration have been dropped out of consideration. Had attention been confined strictly to the running car the results would be changed slightly; the  $\text{CO}_2$  would be a little lower and the equivalent air supply proportionately higher.

As a general rule it is found that the  $\text{CO}_2$  in the air of the berths and in the air of the aisle follow each other consistently in successive determinations, that of the berths averaging a little higher, as would be expected from the fact that the inflowing air from end passageways is not likely to enter them, but to be mixed in the aisles with the contaminated air that flows out from them. This consistency is well shown in Chart 2, in which Experiments 5 and 6, selected because they show the longest series of determinations, are graphically represented. The relation represented in

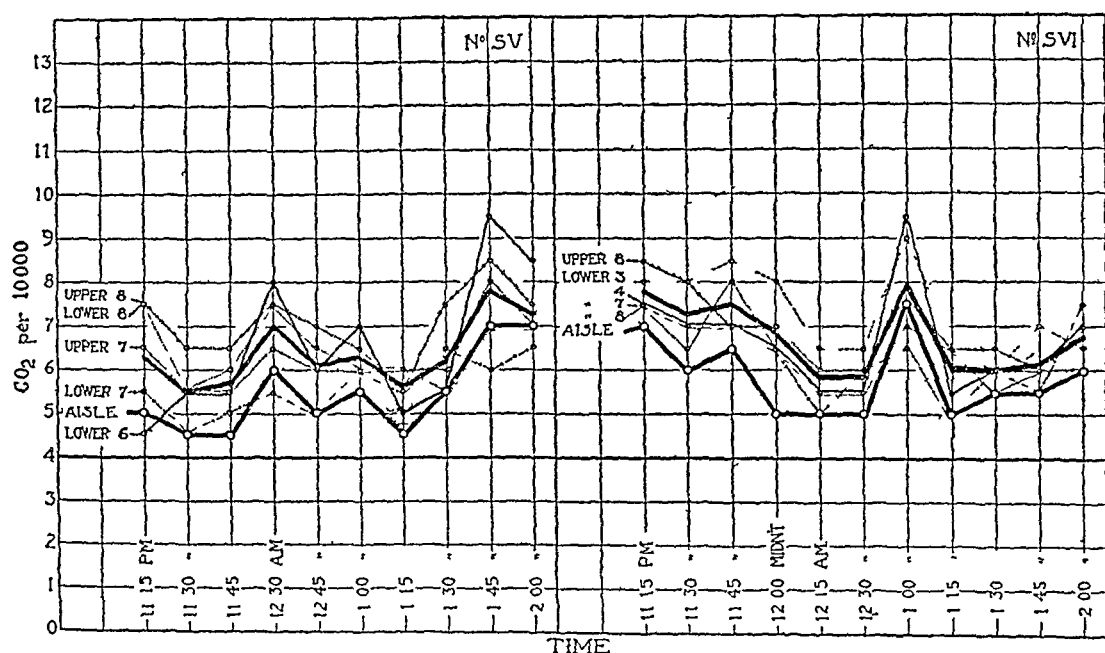


Chart 2—Graphic representation of Experiments 5 and 6, showing consistent relation of  $\text{CO}_2$  in aisle and berths. The lower heavy line represents the findings in the aisle, the upper heavy line the average in the berths, and the broken lines the findings in individual berths. The relation shown here is that which is usually found.

this chart is that which generally obtains, though it occasionally happens that the findings are so varied as to show little if any of such consistency. By far the most striking example of this I am able to produce is shown in Chart 3, in which Experiments 11 and 12 are represented. These two cars were on the same train and were examined at approximately the same time. Two lower berths are here represented in which the  $\text{CO}_2$  momentarily reached 14 parts per 10,000 of air, the only instances but one in which it passed 12. It should be noted also that lower berth seven, shown at the right, shows the highest average  $\text{CO}_2$  (10.71 per 10,000) of any berth of the whole series. It is the only one reaching an average of



10 parts per 10,000, except one berth in Experiment 22, wherein they all ran much above the general average

From what has preceded it is seen that the air supply to the breathing zone of the steel car, constructed without deck-sashes, is materially increased over that of cars similarly equipped as to exhaust ventilating devices, but built with deck-sashes in the ordinary way This increased ventilation is much more noticeable in the air of the aisles than in that of the berths, it results in a somewhat greater difference between the average CO<sub>2</sub> of the aisle and berths than was found in the previous series,

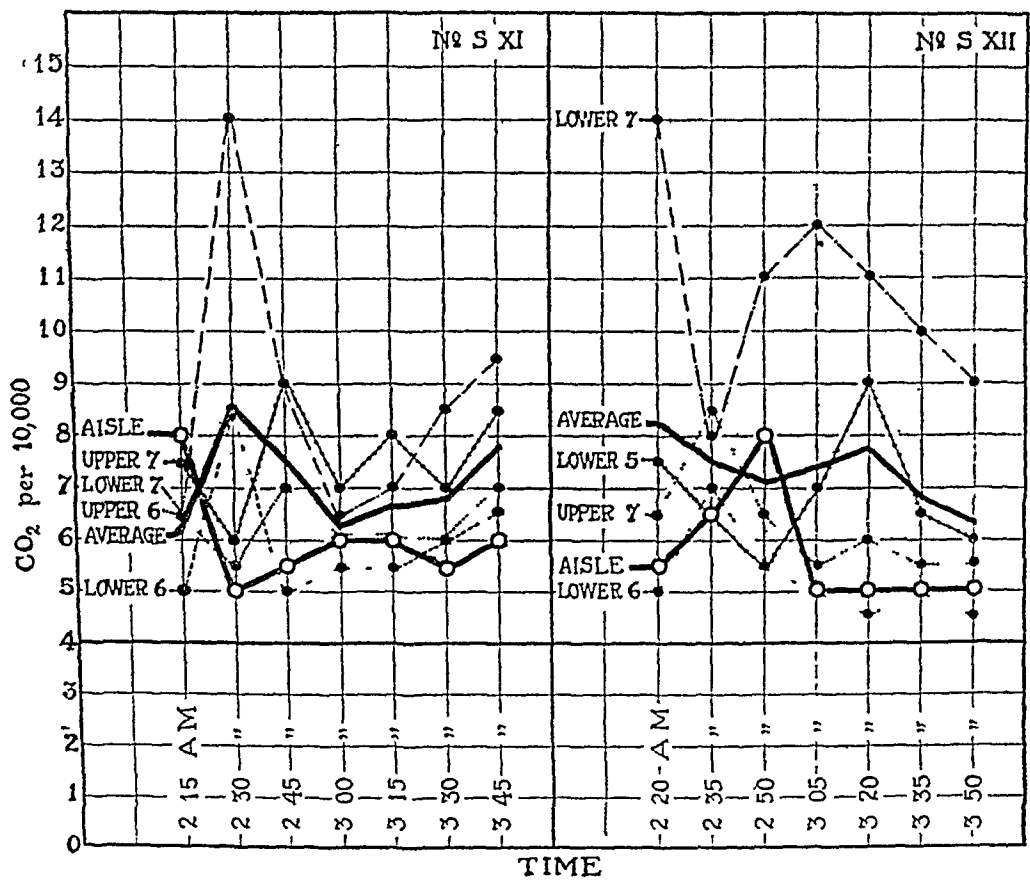


Chart 3—Graphic representation of Experiments 11 and 12, showing inconsistent relation of CO<sub>2</sub> in aisle and berths. The lower heavy line connecting open circles represents the findings in the aisle, the upper heavy line the average for the berths. The lighter lines represent individual berths.

which is interpreted to mean that more air flows from the end doors and passageway windows into the body of the car by reason of there being no crevices at the top to supply the exhaust demand of the ventilators. It is probable that the power of exhaustion developed by these ventilators is very slight as measured by differences of the internal and external barometric pressure. They no doubt act mainly by furnishing a ready exit and continuous outflow of that air forced in by the wind, preventing its damming back near the places of entrance. In this way a constant

upward movement of the incoming air is assured, and this leads to a constant and equalized renewal of the air in the lower levels

#### HYGIENIC CONSIDERATIONS

The principles which should govern the application of ventilating procedures, and the more important experimental evidence on which these are based, have been previously discussed<sup>10</sup> It is not necessary to make further reference to the history and literature of the subject in this place

Until very recent years our knowledge of the hygienic principles of ventilation has been exceedingly imperfect, and our opinions largely erroneous It must be confessed that the subject is still in a rather chaotic condition, but order is beginning to come out of this chaos, if indeed it is not already fully established for those who have carefully studied the excellent experimental work of many investigators who have busied themselves to answer questions concerning why we must ventilate, what are its effects, how are these produced, and on what failures depend. Failures there have been without number, and these, too, when, according to the hygienists, the requisite quantity of pure air was introduced It took the physiologists to answer our questions and to rid us of old and erroneous conceptions The subject has been most clearly set forth, and much new experimental evidence has been added, in a recent communication to the Royal Society of Arts by Professor Leonard Hill,<sup>11</sup> of London

On the basis of well controlled experiments, the following statements seem to be entirely warranted.

1 All trustworthy evidence goes to show that the normal expired air contains no volatile poison<sup>12</sup> and that it is not capable of harming the

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10 In the article referred to in Note 1 and in the Report of the Committee on the Ventilation of Cars, Transactions of the Section on Preventive Medicine and Public Health of the Am Med Assn, Chicago, 1911, p 177

11 Hill and Flack The Influence of Ozone in Ventilation, Jour Royal Society of Arts, London, Feb 9, 1912, p 344

12 Mention should be made in this connection of the recent work of Rosenau and Amoss, "Organic Matter in the Expired Breath," Jour Med Research, 1911, xv, 35 On the basis of the very delicate anaphylactic reaction they have made experiments which would seem to indicate that organic bodies belonging to the protein group may be present in the breath of healthy people, and they express the opinion that these bodies may be harmful when rebreathed

In the air of the lungs any such volatile proteid would be constantly present in fifty or one hundred times greater concentration than in the air of occupied rooms since the air of such rooms does not ordinarily contain more than 1 or 2 per cent of expired air The air which has been expelled from the alveoli and has lodged in the upper air passages during expiration, is drawn back into the alveoli during inspiration The volume of this "dead space" amounts to about one-third of the whole volume of normal quiet inspiration, consequently, the normally inspired air is about one-third expired breath The reexpiration of expired air

human organism when rebreathed under the ordinary conditions of ventilation

2 The increase of carbon dioxide and the decrease of oxygen have nothing to do with the ventilation problem under normal conditions, or with the subjective or objective effects of close air. Carbon dioxide is a necessary constituent of the air of the lungs, it is not to be considered as a poison or the index of a poison. Its proportion in the air of a room is a convenient and fairly accurate index of the quantitative air supply.

3 Air performs for the body a physical function (heat-abstraction) which is quite as important as its chemical function (oxygen-supplying).

4 The ordinary defects of ventilation lie with the physical function of the air and not with the chemical.

5 Temperature, humidity and air movement are the physical qualities of the air which are of importance in this relation.

6 The success of ventilation depends on whether or not these physical qualities of the air are so regulated as to maintain its physical function of heat abstraction without embarrassment to the reflex mechanism for the regulation of body temperature. "The good effects of efficient ventilation and of out-door air depend on the coolness, the relative humidity and the motion of the air and the ceaseless variation of these qualities" (Hill).

These six statements, then, are the main items of the code which should govern attempts to ventilate. We may not go into the practical details of their application here, but it will be noted that quantity of air as a measure of ventilation efficiency is to a large degree lost sight of while the physical qualities of the air as they affect its ability to absorb body heat come strongly forward. The hygienic value of ventilation for the purpose of supplying chemically pure air is much less than has been generally supposed. It should now be looked on as a process to be carried out in the interest of the heat economy of the body. Metabolism is greatly influenced by the rapidity of heat dissipation, and this is controlled by external physical conditions.

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appears to be a conservative and a necessary process. It is a well known fact that the pulmonary ventilation is increased and decreased reflexly to maintain a relatively constant pressure of  $\text{CO}_2$  (about 5 per cent of an atmosphere) in the alveolar air. Our hypothetical poison could not become concentrated in the surrounding air unless the  $\text{CO}_2$  also became concentrated, and then the larger respiratory ventilation due to the increased  $\text{CO}_2$  would affect the concentration of both bodies in the alveolar air in equal proportion. The increase in pulmonary ventilation which would be made necessary by the presence of 2 or 3 per cent of expired air in that which is being breathed, in order to maintain what we must, in the nature of things, look upon as the normal dilution of the alveolar air, is very small. It amounts to no more than 3 or 4 per cent, whereas the possible increase is as many hundred per cent. Such an increase ought to lie well within our "margin of safety."

The great purpose of ventilation is the maintenance of health. This is, in general, accomplished by the maintenance of comfort, for to maintain a comfortable atmosphere is practically to maintain a healthful one. To this end the regulation of temperature and air movement are of the greatest interest and importance, as to the necessity of adding humidity to naturally dry air which has not been superheated, we really know very little. Professor Hill<sup>11</sup> has expressed the opinion that slight but constant changes of temperature and motion in the surrounding medium, leading to constant readjustments of the heat regulating mechanism of the body, are a very important factor in obtaining good results, and he very justly objects to the impulsion of hot air into a room as "the most objectionable of all systems of ventilation." He believes that "a cool air and radiant heat are the ideal." Cold air entering in small jets, and direct radiation, with the irregular and constantly changing convection currents, fulfill the desired conditions well.

It is on such a basis of cause and effect that cars ventilated by the method we have been considering are found to be effectively ventilated from the standpoint of air-comfort and the feeling of bodily well-being. The air supply is always adequate to prevent monotony and stagnation of the conditions surrounding the skin, yet the streams of incoming cold air are individually of such small volume, and take on such irregular and diffuse movement into the stiller body of air within, that the discomfort of draughts is almost entirely avoided. There was no report of discomfort—of so-called "stuffiness"—in the series of cars herewith presented. It will be seen by consulting the tables that their temperatures were always low. When trouble arises it is invariably connected with too much heat. When the temperature is low ventilation always seems to be good, regardless of the amount of respiratory contamination, when the temperature is high ventilation always seems to be bad, regardless of the chemical purity of the air. These are statements which have been amply verified by a long list of observations, comfort and air purity have little or no relation, but comfort and air temperature and motion are very closely related. The delicate sensory nerves of the skin have much to do with the feeling of comfort or discomfort. The judgment arrived at by means of our sensations is in the main a correct one, the air is bad or it is good, just as the sensations indicate, but it is bad or it is good in a physical and not in a chemical sense.

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## A MODIFICATION OF THE TECHNIC OF THE WASSERMANN REACTION

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The "Wassermann" blood test for syphilis is now generally recognized as a valuable aid to the clinician, not only in the diagnosis of the disease, but often as an indicator of the effect of treatment. It is not, perhaps, so generally appreciated, however, that the test, in order to be of real value, must be so carried out that a "positive" reaction will be obtained only in syphilis and in certain other conditions that are readily distinguished from syphilis. No one, thus far, has succeeded in so improving the efficiency of the test that in every case of syphilis with apparent lesions a positive reaction is obtained so that as a diagnostic means a negative "Wassermann" reaction offers no guarantee of the absence of luetic infection, but properly performed, the test, when it results *positively*, must be expected to indicate either syphilis or certain other easily recognized conditions, such as leprosy, malaria, frambesia, paroxysmal hemoglobinuria and probably lead-poisoning.

It follows, therefore, that no modification of the original technic of the Wassermann test can be adopted if, with its use, any positive reactions are encountered in diseases other than those mentioned, and this policy would have to be adhered to even if the modifications proposed promised a great increase in the number of positive reactions obtained in known cases of syphilis.

A number of grave defects attach to the technical procedure originally recommended for the performance of Wassermann test, all of which are due to the impurities contained in the originally prescribed "antigen" preparations (i e, the carbolized watery extract or the alcoholic extract of the liver of a syphilitic fetus). These impurities may interfere in three ways with the performance of the test (1) by exerting a directly anticomplementary influence during the period of fixation, (2) by exerting a hemolytic influence on the blood corpuscles that are used as indicator of the reaction, and (3) by causing a pseudoreaction with the serum of individuals who are neither syphilitic nor subject to any of the other conditions that are mentioned above.

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The first two of these three disturbing actions of the impurities contained in the fetal liver extracts are avoided by selecting for test that quantity of extract which, in double amount, is neither hemolytic nor anticomplementary. The use of this quantity of extract, however, is attended with the third disturbing action and for the elimination of that source of error it has been found necessary to heat the sera to be examined for one-half hour at 50 C<sup>1</sup>

One of the earliest modifications of the "Wassermann" technic was the substitution of an alcoholic extract of normal organs—for example, the heart muscle of the guinea-pig—for the extracts of syphilitic fetal liver. The most extensive studies of both syphilitic and non-syphilitic organ extracts in their "antigenic" capacity were made by Noguchi, who showed that the "antigenic" function of all the extracts resides solely in the lipid fraction, and that the process of separating the lipoids from the extracts eliminates to a large extent the disturbing impurities.

On the basis of this important discovery Noguchi recommended the use of the isolated lipoids, 1 e, the ether-soluble, acetone-insoluble fraction of an alcoholic organ extract as "antigen." Noguchi at first believed that when the isolated lipoids are used as "antigen" in the Wassermann test the sera to be examined could be used without the usual heating at 50 C, but other workers<sup>2</sup> who employed the isolated lipoids found that these also, when used according to the original prescription of the Wassermann technic—1 e, as regards quantity—gave spurious positive reactions with unheated sera. For this reason, as well as on account of the practice of many workers of storing the sera for several days before examining them (during which time they often become anticomplementary), it is customary, also when the isolated lipoids are used as "antigen," to heat the sera.

Our own experiences with the isolated lipid "antigen," which are described in detail elsewhere,<sup>3</sup> have convinced us that *when this "antigen" preparation is used according to the method originally prescribed for the performance of the Wassermann test, its one great advantage over the original organ extract is in part sacrificed and a new source of error is introduced*

The sole advantage of the isolated lipoids over the original organ extracts as an "antigen" preparation lies in the availability of the "antigenic" substances in the former preparation for use in *much greater quantity* than is possible with the latter preparation. This advantage has, however, a two-fold application. We have found, in the first place, that in a considerable proportion of luetic cases—usually

1 In some laboratories higher temperatures (54 to 56 C) are employed.

2 See article by MacRae, Eisenbrev and Swift, THE ARCH. INT. MED., 1910 vi

3 Zeitschr. f. Immunitätsf., 1912, xiv, p. 139

those exhibiting lesser lesions or those that have received only mercurial treatment—a positive reaction is obtained when a larger quantity of the isolated lipoids is used, but the test results negatively with smaller quantities, *i. e.* with quantities that represent the amount of “antigenic” substance that is used in the originally recommended procedure

As we have just indicated, there is another way in which the availability of the isolated lipid “antigen” for use in relatively large quantities can be applied to advantage in carrying out the Wassermann test. In determining the reacting strength of immune sera by means of the Bordet-Gengou technic—which is the prototype of the Wassermann technic—it is customary to estimate the relative values of such sera according to the smallest amount of the respective antigen with which, under like conditions, complete complement fixation is produced. Since the mechanism of the Bordet-Gengou reaction and that of the Wassermann reaction are undoubtedly identical, it must be possible to apply, in the latter test, the same principle of quantitative comparison that is used in the former.

This plan was suggested a number of years ago by Neisser, Bruck and Schucht, but in the absence of any further publication on the matter by these authors it may be assumed that their attempt in this direction was not successful.

Their failure can be easily explained.

An examination of their published protocols discloses the fact that, owing to the admixture of the usual impurities in their standard “antigen” preparation, which was an alcoholic extract of the liver of a syphilitic fetus, they were limited to the use of only eight times the smallest amount of “antigen” with which, in cases of untreated secondary syphilis, complete complement fixation could be produced. With an “antigen” preparation limited to such a narrow working range, it was not possible to apply the quantitative method of the Bordet-Gengou test.

The isolated lipid “antigen,” on the other hand, can be safely used in a quantity that is at least 500 times the minimum complete fixing unit—as determined in cases of untreated secondary syphilis—and with this preparation, therefore, the quantitative technic of the Bordet-Gengou test becomes directly applicable to the Wassermann test.<sup>4</sup>

If then, as is commonly done, the isolated lipid “antigen” is employed for the Wassermann test in only one quantity—*i. e.*, one-half of the largest amount that, by itself, is neither hemolytic nor anti-

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4 It must be emphasized here that whether the reacting strength of luetic sera as determined according to the minimum fixing quantity of “antigen” does or does not always coincide with the degree of severity of the syphilitic process that exists at the time of the examination, the result of such a determination does give a true index of the concentration of the reacting substances in the sera.

complementary—the advantage of the quantitative method of the Bordet-Gengou test is sacrificed

But the sacrifice of the quantitative technic is not the only objection that must be urged against the application of the Wassermann prescription to the use of the isolated lipoid “antigen” We have mentioned the experience of MacRae, Eisenbrey and Swift, who found that even with the isolated lipoid “antigen,” unless the sera to be examined are heated, “positive” reactions are sometimes obtained in many diseases other than syphilis<sup>5</sup>

The practice of those who use the isolated lipoid “antigen” of heating the sera to be examined in order to avoid such spurious positive reactions, greatly exaggerates a new source of error—one that is not encountered when the smaller quantities of the “antigenic” substances are used, as under the original Wassermann technic—which attaches to the use of the isolated lipoid “antigen” The source of error referred to is the familiar prezone phenomenon of wanting reaction, which occurs in the testing of specific antisera when either of the two reacting substances, antigen and antibody, is combined with the other in a quantity that is in excess of a definite proportion

The prezone phenomenon that is sometimes produced in the performance of the Wassermann test is due to the use of a relative excess of the “antigenic” substances It is much more frequently met with when the sera to be examined are heated, but it has been observed by us in twelve instances in which the sera had not been heated

The source of error presented by the prezone phenomenon occurring in the Wassermann test can be easily eliminated by carrying out each test with descending quantities of the “antigen,” so that it is not necessary, only on account of this possible fallacy, to omit the heating of the sera That the custom of heating the sera should be discarded when it is possible is, however, evident in view of the well-known fact that heating considerably reduces the reacting power of luetic sera

As a matter of fact, the heating of the sera *can* be dispensed with, for we have found an equally certain and much simpler way to accomplish the end for which the heating was usually performed, namely, to avoid the spurious “positive” reactions of diseases other than syphilis We have observed, in a series of several hundred examinations, that whereas with unheated sera 0.2 c c of a 1 to 10 dilution of our 2 per cent lipoid solution often gives complete fixation in many conditions other than syphilis, no such spurious reaction is produced by 0.1 c c of that dilution of the lipoids With one exception all of the fixations produced with the latter

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5 Notwithstanding this serious complication these writers conclude that “the Noguchi method, using *active* serum gives the most sensitive reaction in syphilis” We have already pointed out the fallacy of this view



quantity of the isolated lipoid "antigen" have been obtained in cases of known syphilis. That one exception was in a case of paroxysmal hemoglobinuria, in which disease the original Wassermann technic produces regularly a "positive" result."

*Instead of heating the sera, therefore, we avoid the spurious or "pseudoreactions" by using about half the prescribed amount of the isolated lipoid "antigen," which, as we have already stated, is 500 times the minimum fixing quantity for secondary syphilis.*

#### SUMMARY

The substance of the preceding discussion may be more briefly presented as follows:

1 Only the lipoid fraction of organ extracts possesses the "antigenic" properties requisite for the performance of the Wassermann blood test for syphilis (Noguchi).

2 On account of the large admixture in the originally recommended "antigen" preparations (i. e., the carbolized watery extract and the simple alcoholic extract of the liver of a syphilitic fetus) of substances not possessing "antigenic" properties, the quantitative limits within which the "antigenic" substances are available for the Wassermann test, are very narrow—4 to 8 units. When such extracts are used for the test the sera must be heated, otherwise positive reactions are obtained in many diseases besides syphilis. The reacting strength of luetic sera is considerably reduced by heating.

3 The quantitative limits within which the isolated lipoid "antigen" is available for the Wassermann test, are relatively wide—at least 500 units—so that with this preparation positive reactions can be obtained with luetic sera with which the test would result negatively if only the relatively small amount of "antigen" available under the original Wassermann procedure was used, furthermore, on account of the greatly extended working-range of the isolated lipoid "antigen" preparation the usual quantitative method of determining the reacting strength of specific antisera according to Bordet-Gengou can be employed.

4 When the isolated lipoid "antigen" preparation is used according to the original Wassermann prescription, "positive" reactions are often obtained with active sera in many diseases other than syphilis. These spurious or "pseudoreactions" can be entirely avoided, without heating the sera, by not using more than about half of the prescribed amount of the "antigen" preparation, i. e., one-fourth instead of one-half of the largest quantity of the preparation that by itself is neither hemolytic nor anticomplementary.

5 When the isolated lipoid "antigen" preparation is used in descending quantities in the Wassermann test, the prezone phenomenon is some-

times observed, which is due to the use of an excess of the "antigenic" substances. This source of error is met with in a considerable proportion of heated luetic sera, and occasionally even when the sera are not heated; it can be avoided only by the use, in each test, of descending quantities of the "antigen" preparation

#### PROPOSED TECHNIC

*Antigen* —The most convenient source of suitable lipoids is the heart muscle of the ox. The muscular tissue is dissected out from the heart of a recently slaughtered ox, and, after being finely comminuted in a meat grinder, is shaken well with about ten volumes of 95 per cent alcohol. The alcoholic extract is filtered after five to ten days and evaporated nearly to dryness with the use of an electric fan. The sticky residue is extracted with ordinary ether and the ether extract again evaporated with the use of the fan, supplemented finally with gentle warming. The resulting residue is then extracted with water-free ether in small quantity and the clear solution obtained by centrifugation is mixed with five volumes of acetone. After thorough shaking the fluid is poured off the waxy precipitate, which is then shaken several times with fresh portions of acetone. The stock solution is a filtered 2 per cent solution of the lipoids in pure methyl alcohol. For each series of tests a fresh emulsion is made by diluting one part, by volume, of the stock solution up to ten parts with physiological salt solution (Ringer's). Of this 0.2 per cent emulsion, 0.4 c.c. has never produced the slightest hemolysis when mixed with 0.1 c.c. of a 5 per cent suspension of sheep's blood, nor is that amount anticomplementary with 0.01 c.c. of guinea-pig's serum (indicator 0.1 c.c. of 5 per cent sensitized sheep's blood).

Some lipid preparations from ox's heart muscle are not capable of functioning as "antigen" in the Wassermann test. Of four such preparations made from four different ox-hearts, one was completely lacking in "antigenic" property. The other three were efficient, and equally so, in that capacity. The "antigenic" property of our first preparation has remained unchanged for more than one year.

In the interest of economy of materials, all the reagents entering into the Wassermann test may be used in one-tenth of the usual quantities. Under this condition we have found that with cases of untreated secondary syphilis, the minimum fixing amount of ox-heart lipoids is frequently as little as 0.0002 c.c. of a 0.2 per cent emulsion, that is, 0.000001 g.

Some of the sera that have been obtained more than twenty-four hours previous to the examination are found to have become anticomplementary, that is, 0.4 c.c. or less, of the diluted serum inhibits by itself the complementary function of 0.1 c.c. of guinea-pig's diluted serum.

In order to remove this anticomplementary property it is necessary to heat such sera for one-half hour at about 50 C. For the exact determination of the fixing strength of a luetic serum, it is, therefore, important that the test be made within twenty-four hours after the blood has been taken, so that the necessity of inactivation may be avoided. If, as we have always done, the reagents entering into the Wassermann test are all used in one-tenth of the usual quantities, the amount of the patient's serum required for such examination is correspondingly reduced, so that sufficient blood for the test can be easily obtained from the ear or finger. Such small amounts (2 c c) are best defibrinated and centrifugated at once. The serum can then be removed with a pipet and is ready for immediate examination.

*Complement*—This function is supplied by 0.1 c c of a 1 to 10 dilution of fresh guinea-pig's serum in physiological salt solution. Whenever this serum is naturally hemolytic for sheep's blood corpuscles, the natural hemolysin is to be removed by the cold separation method—one to two hours at 0 C. in contact with washed sheep's corpuscles.

*Indicator*—Two per cent sheep's blood corpuscles sensitized with two to three minimum hemolytic doses of immunized rabbit's serum are used as indicator. To each tube is added 0.25 c c of this suspension, representing 0.1 c c of the usual 5 per cent suspension.

When the test was carried out according to the plan that we have described, we were not able to observe any essential difference in the results that could be due to differences, within the limits given above, in the degree of sensitization of the blood corpuscles that were used as indicator of the reaction. The sensitization should be so adjusted to the complementary activity of the guinea-pig's serum that not more than 0.025 c c of that serum diluted 1 to 10 will be required, and that not less than 0.0125 c c will be able completely to hemolyze 1 unit (0.25 c c of a 2 per cent suspension) of the sensitized blood cells.

In the practical performance and reading of the Wassermann test we proceed as follows:

1. All the reagents entering into the reaction of fixation can be most conveniently diluted 1 to 10 with physiological salt solution. The sensitized sheep's blood suspension may be 2 per cent (unit=0.25 c c) or 5 per cent (unit=0.1 c c).

2. Five different amounts of a 0.2 per cent emulsion of ox-heart lipoids are to be combined with 0.2 c c of the patient's diluted serum and 0.1 c c of the diluted guinea pig's serum. The five amounts of antigen are 0.1, 0.05, 0.02, 0.01 and 0.001. A series of examinations with non-luetic sera should be made for the purpose of determining the lower limit of pseudo-reaction.

3. If complete fixation of complement occurs with all of the five quantities of 'antigen' or with only the smallest two or three quantities, we report a "strongly positive" reaction, if with 0.001 c c hemolysis has not been prevented, but fixation has occurred with all the other combinations or with the lesser one or two quantities of "antigen," we report a "positive" reaction, if hemolysis is not prevented with 0.001 nor with 0.01 c c, but fixation occurs with any of the other amounts of the "antigen," we report a "weakly positive" reaction.

We have never met with an occasion for reporting a "doubtful" reaction

We have confirmed the observations of Jacobsthal and of Guggenheimer, that with some luetic sera a positive Wassermann reaction can be obtained when the "incubation" for fixation is carried out at ice-box temperature, whereas the test as usually performed results negatively. The reverse of this, also, has been found, in some instances, to be true.

In view of these facts it is necessary to perform each test in duplicate series, one for fixation at ice-box temperature, and the other for fixation at 37 C. The period of incubation for fixation at low temperature may be twelve to eighteen hours (conveniently over night).

In the table are given examples of the results that we have obtained with our technic, together with our "reading" of them.

TABLE GIVING EXAMPLES OF THE RESULTS OF THE WASSERMANN REACTION OBTAINED UNDER AUTHORS' TECHNIC, CLASSIFIED ACCORDING TO REACTING STRENGTH OF THE SERA

Indicator 0.25 cc of 2 per cent sheep's corpuscles. In each tube 0.02 cc of patient's serum + 0.01 cc of guinea-pig's serum

—————0.2 per cent Emulsion of Ox-Heart Lipoids—————

0.1 cc	0.05 cc	0.02 cc	0.01 cc	0.001 cc	
0	0	0	0	0	} Strongly positive reactions
++++	++	0	0	0	
++++	++++	++	0	0	
0	0	0	0	++++	} Positive reactions
++++	++	0	0	++++	
++++	++++	++	0	++++	
0	0	0	+++	++++	} Weakly positive reactions
0	0	+	++++	++++	
0	++	++++	++++	++++	
++++	0	0	++	++++	
++++	+++	+	+	++++	

++++ = complete hemolysis, +++ = very strong hemolysis, ++ = partial hemolysis, + = slight hemolysis

# STUDY OF THE CHEMISTRY OF RENAL CALCULI

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Rowlands,<sup>1</sup> in his examination of twenty-two stones, came to the following conclusions that renal calculi are composed almost entirely of calcium oxalate, that uric acid is almost always absent, or present in very small traces, that phosphates are commonly present

Mackarell, Moore and Thomas,<sup>2</sup> following the investigations of Rowlands, concluded that these results have a marked bearing on the calcium metabolism in gout and allied conditions. They examined twenty-four renal stones and they corroborated the findings of Rowlands. They recommended that when a calculus has been obtained by operation or otherwise, it should be analyzed, and if it is found to be composed of calcium salts, the patient should be put on a course of *acid* treatment and not alkaline medications, as has been the custom.

I have examined a series of sixteen stones from patients of the Mount Sinai and various other hospitals in New York City. The patients were immigrants to the United States from all parts of Europe, most of them from Russia and Austria. From the histories of these patients, no evidence of gout or a gouty diathesis could be obtained. They were all of the poorer class, living in the crowded tenement districts of New York and not at all addicted to high living, or to the use of wines and ales.

The results of Rowlands and Moore are quite startling. Every textbook states that calculi of uric acid, or of the salts of uric acid, are by far the most frequent. Osler, Wood, Hammarsten, Halliburton, Wells, Allbutt, etc., invariably introduce their remarks on the chemistry of renal stones by some statement that the urates are the most frequent components. The quantitative examinations that have been made up to now would impress one with the certainty that the chemistry of the nephroliths was an established fact, and indeed, when I first read the article of Rowlands and the one by Mackarell, Moore and Thomas, I doubted the general application of their findings.

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\*From the laboratory of Biological Chemistry of Columbia University, at the College of Physicians and Surgeons, New York

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1 Rowlands, J. S. *Biochem Jour*, 1908, *iii*, 346

2 Mackarell, W. W. Moore, B., and Thomas, W. T. *Biochem Jour*, 1910, *v*, 161

It is interesting to note the results of previous examinations Brande,<sup>3</sup> in a series of 150 cases, found that sixteen calculi were composed wholly of uric acid, while the rest contained some Fourcroy and Vauquelin<sup>4</sup> found lithic acid in the greater number of 500 stones Pearson<sup>5</sup> found this acid in the majority of 300 concretions Henry states that of 187 stones, 158 had uric acid nuclei Of 545 cases of stone, Ultzman<sup>6</sup> found that 80.9 per cent contained a nucleus of uric acid, while 5.6 per cent were composed of calcium oxalate Recently chemical analyses have been made by Morris, Israel and Johnson<sup>7</sup> with the unvarying conclusion that urates predominate in their composition

Young,<sup>8</sup> in Osler's Modern Medicine, says "Such methods of quantitative chemical analysis of calculi as have been used until quite recent years were so inexact that they sometimes furnished misleading information" He continues to say, "The physical characteristics of calculi vary greatly and are somewhat indicative of their composition On these rather than on chemical analysis, have been based many statements as to the nature of renal calculi"

In the series of sixteen cases that I have analyzed, no conclusions could be drawn from the appearance and consistency of the stones as to their chemical composition Some, that were quite soft and easily pulverizable, were almost wholly composed of calcium oxalate Others, that were white and irregular and of excessive hardness contained a high percentage of uric acid The characteristic "mulberry stones," "stag-horn," or coral calculus, and "jack-stone" calculus did not appear in this series

As Rowlands suggested, the rate and process of formation of the stone have more to do with the hardness or softness of the calculus than its chemical composition

#### METHODS OF ANALYSIS

The methods of analysis followed were almost identical with the one suggested by Mackarell, Moore and Thomas

a Physical Characteristics The size, shape, color, and consistency of the stones were noted The method used to determine the hardness or softness of the stone was by simple crushing, noticing the force exerted in breaking up the stone

b The murexid test for uric acid was performed on each stone, and positive results were obtained in all cases

c Chemical Composition The stone after being finely pulverized, was carefully weighed in a drying flask (whose weight was previously found), and then dried in an oven for about two hours at a temperature of 100 to 105 C, and again weighed, the loss in weight being taken as moisture

3 Brande Hooper's Med Dic 1820

4 Fourcroy and Vauquelin Ann d chem, 1805, lvi, 258

5 Pearson Tr Roy Philosoph Soc 1798 xv, 59

6 Ultzman Cited after Hammarsten's Physiol Chem 1908

7 Johnson New York Med Jour, 1905, lxxxvii, 209

8 Young Osler's Modern Medicine, 1908, vi, 316

*Quantitative Determination of Uric Acid*—A quantity varying according to the amount of the stone available, was taken and accurately weighed. This was then placed in a porcelain dish, treated with hydrochloric acid (14) and heated on a steam bath until as much as possible had been dissolved. It was then filtered through a weighed Gooch filter, the residue well washed, and then dried at 100 C for from one to two hours until the weight was constant, this weight was recorded. The residue in the Gooch, asbestos and all, was next treated with strong sulphuric acid. The acid was then diluted and titrated with  $n/20$  potassium permanganate solution, 1 cc of which is equal to 0.0075 gm of uric acid. A control was always performed with the sulphuric acid and water in order to get an accurate result, the amount of permanganate taken by the control being deducted from the result of the former titration.

*Quantitative Determination of Calcium Oxalate*—The filtrate obtained after digesting the stone with hydrochloric acid was next mixed with the washings of the residue, and ammonium chlorid and ammonium hydroxid added in excess. The precipitate obtained was filtered and thoroughly washed until free from chlorids (the washings being tested with silver nitrate). The filtrate and the washings were boiled and ammonium oxalate added until precipitation was complete. The precipitate was allowed to stand twenty-four hours until it had completely settled. The liquid was filtered off, and the precipitate washed by decantation until free from chlorids, which would otherwise interfere with the permanganate titration. The precipitate was washed from the filter paper into a beaker, first by means of hot water and then with 10 per cent sulphuric acid and finally all the acid was washed into the flask by means of hot water. The whole was then mixed, cooled and made up to 1,000 cc. Of this 50 cc were pipetted off, and titrated at a temperature of 65 C with  $n/20$  potassium permanganate solution, 1 cc of which is equivalent to 0.0019 gm of calcium, or 0.00608 gm of calcium oxalate.

*Quantitative Estimation of Total Nitrogen*—Another portion of the stone was then weighed out, and placed in a Kjeldahl flask, and the total nitrogen determined by the Kjeldahl process.

*Quantitative Estimation of Phosphates*—Phosphates were estimated as phosphorus pentoxid by the following method. A portion of the powdered stone having been weighed, was put into a Kjeldahl flask and 20 cc of a mixture of equal parts of concentrated sulphuric acid and concentrated nitric acid were added. The Kjeldahl flask and contents were then heated until colorless. This usually took thirty-five minutes. Five drops of fuming nitric acid were then added and it was again heated until colorless. The contents of the Kjeldahl flask were cooled and then diluted with water. It was next neutralized with ammonium hydroxid and then reacidified with concentrated nitric acid. The mixture was then put into a beaker and to this were added 50 cc of a 60 per cent solution of ammonium nitrate, and 25 cc of a 10 per cent solution of ammonium molybdate. This was allowed to stand 12 to 24 hours at 60 C and was then filtered. The precipitate was dissolved in ammonium hydroxid, and 10 cc of concentrated hydrochloric acid were added. To this were added 25 cc of magnesia mixture. After standing fifteen minutes an excess of ammonium hydroxid was poured in and the mixture allowed to stand for twenty-four hours. The precipitate was filtered on a weighed Gooch filter, burnt, and from the weight of the pyrophosphate of magnesium the weight of phosphorus pentoxid was estimated.

Most of the stones examined were mainly composed of calcium oxalate. The percentage of calcium oxalate varied from 29.5 per cent to 94.7 per cent. The physical appearance and the consistency of the stone were not at all indicative of its chemical constituents. The one which was 94.7 per cent oxalate was a ureteral stone, brown in color, very irregular in shape, very soft and brittle. The stone which contained 29.5 per cent oxalate was very hard, dark brown in color, spheroidal, with many

irregular projections—the only stone that could be called “mulberry”-like—and it contained 74.6 per cent uric acid and 56.2 per cent phosphorus pentoxid

All the stones gave the murexid test, so that either uric acid or its salts were present in each case. The statement made by Rowlands, and later by Mackarell, Moore and Thomas, that uric acid is usually absent in urinary calculi must, therefore, be modified. Though it is present ordinarily in very small amount, still its presence must be recognized. The amount of uric acid found, ranged from 40.6 per cent to 0.2 per cent. Nevertheless, the amount of uric acid usually present is negligible as compared with the calcium oxalate. The urate stone, so graphically depicted in the text-books, is a very rare occurrence in the quantitative laboratory. The total nitrogen determination, when calculated as uric acid, rarely exceeded the amount of this acid estimated according to the method used by Moore.

Phosphates were found in nearly all the calculi, and in some stones the percentage of the phosphates was very high. No carbonates were found. This quite agrees with Rowlands, who found phosphates in traces in nearly all the stones and carbonate in only two out of a series of twenty-two examinations.

One of the conclusions that Mackarell, Moore and Thomas draw from the fact that they did not find uric acid in renal calculi is, that gout may be a disease due to deficient calcium metabolism, and that it is rather this deficiency than the disturbance in the uric acid output that has to be treated. This assumption is not warranted. Renal calculus is not always, nor even usually, due to gout. The fact that gouty patients sometimes suffer from gravel cannot be brought forward as an argument that whatever is the metabolic derangement in lithiasis is also the causative factor of podagra. Sir William Roberts<sup>9</sup> states that the impression that gouty individuals invariably suffer from calculus disease and the impression that patients who suffer from nephrolithiasis are also afflicted with gout, are erroneous. In certain portions of India, gravel in the urine and stone in the kidney are very common complaints and still gout, or the gouty diathesis, is unknown. In Norfolk<sup>10</sup> calculus disease is very common, while podagra is rare. The reverse is the case in other portions of England. As Fagge<sup>11</sup> asserts, there are certain districts where travelers (not at all gouty) acquire lithiasis, and are cured only on removal from the territory.

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<sup>9</sup> Roberts. Allbutt's System of Medicine

<sup>10</sup> Yalloy. Tr. Roy. Philosoph. Soc., 1839, LXXXIX, 149

<sup>11</sup> Fagge. Cited from Osler's Modern Medicine



## DETAILS OF ANALYSIS OF THE SIXTEEN CALCULI

The subjoined tables record the results obtained. A brief summary of the history of each patient (when a history could be obtained) and a macroscopic description of each calculus are also given.

**CALCULUS 1—Gross Appearance**—The stone was in two portions. Each one was irregularly semilunar, very hard, white and smooth. The stone weighed 12.0446 gm.

**Chemical Examination**—In 0.942 gm. of the powdered stone there were 0.3532 gm. calcium oxalate or 37.4 per cent and 0.034 gm. uric acid or 3.59 per cent. It contained 51.59 per cent phosphorus pentoxide—0.7569 gm. of the stone gave 0.3898 gm. of phosphorus pentoxide.

**CALCULUS 2—History**—Patient C. I. of Mount Sinai Hospital. Stone given to me by Dr. Morris H. Kahn. Ureteral stone. Patient had characteristic renal colics and was operated on by Dr. Brettauer. She is Russian by birth.

**Gross Appearance**—Small, irregular stone, very brittle and soft, brown in color.

**Chemical Examination**—The stone weighed 0.5114 gm., of which 0.0210 was moisture, so that the dried stone weighed 0.4904 gm. The moisture was 4.1 per cent. From 0.1399 gm. of the stone, 0.13254 gm. calcium oxalate was obtained or 94.7 per cent, and 0.003075 gm. uric acid or 2.1 per cent. The yield of phosphorus pentoxide from 0.1174 gm. was 0.0061 gm. or 5.3 per cent.

**CALCULUS 3—History**—Stone was given to me by Dr. M. H. Kahn. Patient was in the Mount Sinai Hospital. Suffered from an attack of pain and hematuria. No history of gout. Stone was removed by nephrotomy.

**Gross Appearance**—A very hard stone with spinous processes. It was dark brown in color and irregularly spheroidal.

**Chemical Examination**—The stone weighed 13.982 gm., and when dry it weighed 13.6805 gm., the moisture being 2.1 per cent. The yield of calcium oxalate from 1.015 gm. was 0.2988 gm. or 29.5 per cent. From the same stone portion 0.07575 gm. uric acid, or 7.46 per cent, were obtained. The phosphates were in excess, 1.3971 gm. of the stone gave 0.78212 gm. phosphorus pentoxide, or 56.2 per cent.

**CALCULUS 4—Clinical history unknown.** Patient, L. M., Jewish, of the poorer class, immigrant to the United States. Stone given to me by Dr. M. H. Kahn.

**Gross Appearance**—The stone was triangular in shape, smooth, hard, grayish in color, and regular in form.

**Chemical Examination**—The stone weighed when dry 0.5940 gm., having lost weight in drying, 0.0069 gm. The moisture was therefore 1.08 per cent. In 0.2340 gm. of the stone there were found 63.4 per cent calcium oxalate and 40.06 per cent uric acid. In 0.1256 gm. of the stone 7.3 per cent phosphorus pentoxide was found.

**CALCULUS 5—History**—Patient, A. S., male, of Mount Sinai Hospital. Long history of pain, hematuria, pyuria, and finally sepsis. Nephrectomy performed on the patient for renal calculus. Stone given to me by Dr. M. H. Kahn.

**Gross Appearance**—The stone was broken into several pieces. It was smooth and irregularly faceted, and whitish yellow in color. Its consistency was very hard.

**Chemical Examination**—The stone weighed, when dry, 14.9483 gm., having lost 0.0477 gm. as moisture, or 0.23 per cent. The stone was almost wholly composed of calcium oxalate—94.1 per cent. Uric acid was 0.2 per cent and phosphorus pentoxide was 6.1 per cent.

**CALCULUS 6—History**—This stone was from the other kidney of the same patient, A. S. (Case 5). A nephrotomy was performed for this stone.

*Gross Appearance*—The stone was quite small, smooth and firm and yellowish-white in color

*Chemical Examination*—The stone weighed 2.4505 gm. Moisture was 3.2 per cent. It is interesting to note that this stone, removed from the same patient as Calculus 5, contained 72.3 per cent calcium oxalate and 23.6 per cent uric acid. This is a remarkable fact, if a diathetic derangement is to be taken as the etiological factor of renal stones. Phosphorus pentoxid was present to the extent of 4.3 per cent.

CALCULUS 7—No history of the patient

*Gross Appearance*—The stone was smooth, round and hard. It was flat and yellow.

*Chemical Examination*—The stone weighed, when dry, 6.0971 gm. Moisture was 1.3 per cent. In 0.4163 gm of the stone, there were 0.385 gm of calcium oxalate or 90.5 per cent and 0.0374 gm uric acid or 9.01 per cent. Phosphorus pentoxid gave a yield of 0.5 per cent.

CALCULUS 8—No history of the patient

*Gross Appearance*—Smooth, white, hard stone

*Chemical Examination*—The stone weighed 4.0349 gm. Its moisture was 0.04 per cent. In 0.5914 gm of the stone, there were found 91.7 per cent calcium oxalate, and 1.01 per cent uric acid. Phosphorus pentoxid was found to be 6.4 per cent.

CALCULUS 9—Stone given to me by Dr J. Rosenbloom. No history of the patient.

*Gross Appearance*—The stone was very hard and very irregular. It was yellowish-white in color.

*Chemical Examination*—The stone weighed 5.7725 gm and the moisture was 0.1324 gm or 0.02 per cent. From 0.9133 gm of the stone were obtained 0.86023 gm of calcium oxalate or 94.2 per cent and 0.0164 gm uric acid or 1.8 per cent. The yield of phosphorus pentoxid was 0.01281 gm from 0.2784 gm of the stone, or 4.6 per cent.

CALCULUS 10—Patient S. S. of Mount Sinai Hospital. Stone given to me by Dr M. H. Kahn.

*Gross Appearance*—A large white stone. It was very hard so that pounding had to be exerted in order to crush it. It was very rough and very irregular. It was composed of three pieces.

*Chemical Examination*—The stone weighed 15.9125 gm. In 0.3136 gm of the stone, there were found 0.2314 gm of calcium oxalate, or 73.8 per cent, and 0.0235 gm uric acid or 7.5 per cent. The yield of phosphorus pentoxid was 20.1 per cent, i. e., 0.4182 gm of the stone gave 0.08405 gm of the pentoxid.

CALCULUS 11—*History*—No history of patient.

*Gross Appearance*—Large white stone, very hard, so that much pounding had to be exerted in order to crush it. It was very rough and very irregular. It was composed of three pieces.

*Chemical Examination*—The stone weighed 15.9125 gm. In 0.3136 gm of the stone, there were found 0.2314 gm of calcium oxalate, or 73.8 per cent, and 0.0235 gm uric acid, or 7.5 per cent. The yield of phosphorus pentoxid was 20.1 per cent, i. e., 0.4182 gm gave 0.08405 gm of the pentoxid.

CALCULUS 12—*History*—Patient was in the Mount Sinai Hospital. Was an immigrant to New York. History of renal calculus symptoms. Stone given to me by Dr M. H. Kahn.

*Gross Appearance*—The stone was brown, light, soft, smooth, and regular and oval in shape.

*Chemical Examination*—The stone weighed 0.9329 gm. Moisture was 0.0041 gm. In 0.2179 gm of the stone there were found 0.17519 gm calcium oxalate—

80.4 per cent—and 0.0224 gm of uric acid or 10.3 per cent. In 0.1745 gm of the stone there were 0.01137 gm of phosphorus pentoxide or 6.5 per cent.

**CALCULUS 13—History**—A ureteral stone, given to me by Dr M H Kahn. It was removed by nephrotomy.

**Gross Appearance**—The stone was in three small portions. It was a very smooth, dark, round calculus, of excessive hardness.

**Chemical Examination**—The stone weighed 0.1612 gm of which there were 91.3 per cent calcium oxalate, 2.46 per cent uric acid, and 5.23 per cent phosphorus pentoxide.

**CALCULUS 14**—No history of the patient. The stone was given to me by Dr M H Kahn.

**Gross Appearance**—The whole stone was rounded, irregular, with spinous projections of the size of a walnut. The portion examined was as white as chalk, brittle in general, though firm in areas, and very irregular.

**Chemical Examination**—The whole stone was not weighed. The portion analyzed weighed 1.6064 gm of which 0.0016 gm was moisture. From 0.2467 gm of the powdered stone, there were obtained 0.17318 gm calcium oxalate, or 70.2 per cent, and 0.0298 gm uric acid or 12.1 per cent. Phosphorus pentoxide was present to the extent of 16.9 per cent.

**CALCULUS 15—History**—Renal stone removed *post mortem* from kidney by Dr J Rosenbloom. No clinical history of patient.

**Gross Appearance**—The calculus was very dark brown, broken in several places and shaped like the pelvis of the kidney. It was very hard and very jagged.

**Chemical Examination**—The stone weighed 12.3471 gm, of which there was 0.3 per cent moisture. The portions examined gave a yield of 90.37 per cent calcium oxalate, 3.4 per cent uric acid, and 6.21 per cent phosphorus pentoxide.

**CALCULUS 16**—No history of the patient. Stone given to me by Dr Rosenbloom.

**Gross Appearance**—Grayish-white brittle stone, rounded, with some projections. It crumbled very easily on the slightest pressure.

**Chemical Examination**—The stone weighed 9.7621 gm. Its moisture was 3.1 per cent. The yield of calcium oxalate from 0.2317 gm of the stone was 0.2114 gm, or 91.3 per cent. The yield of uric acid from the same stone portion was 0.0156 gm or 7.2 per cent. The phosphorus pentoxide was 2.1 per cent.

TABLE OF PERCENTAGE COMPOSITION OF THE CALCULI

Number	Weight	Moisture, Per cent	Ca Oxalate, Per cent	Phosphorus Pentoxide, Per cent	Uric Acid, Per cent	Total Nitrogen, Per cent
I	12.0446	6.11	37.4	51.59	3.59	0.91
II	0.5114	4.1	94.7	5.3	2.1	1.2
III	13.982	2.1	29.5	56.2	7.46	4.2
IV	0.6009	1.08	63.4	7.0	40.06	27.3
V	14.998	0.23	94.1	6.1	0.2	1.3
VI	2.4505	3.2	72.3	4.3	23.6	12.9
VII	6.175	1.3	90.5	9.01	0.5	4.21
VIII	4.0349	0.04	91.7	6.4	1.01	0.76
IX	5.7725	0.02	94.2	4.6	1.8	1.02
X	2.8304	0.15	81.6	9.5	9.3	3.72
XI	15.9125	0.4	73.8	20.1	7.5	3.1
XII	0.9329	0.43	80.4	6.5	10.3	4.62
XIII	0.1612	0.05	91.3	5.23	2.46	1.09
XIV	1.6064	0.099	70.2	16.9	12.1	4.3
XV	12.3471	0.3	90.37	6.21	3.4	2.58
XVI	9.7621	3.1	91.3	2.1	7.2	5.81

In the paper by Mackarell, Moore and Thomas, the authors suggest that gouty tophi may be composed almost entirely of calcium oxalate, in spite of the prevailing idea that they are composed of the salts of uric acid. They had no material on hand and their suggestion was purely hypothetical. I have been able to investigate the composition of three tophi—two from the lobules of the ear and one from a gouty concretion in a joint. The concretions, however, were in such small amounts that no quantitative examination could be made. I, therefore, did only the murexid test, *and it gave a negative result in each of the three cases*. H. Matthes and E. Ackerman<sup>12</sup> lately examined a very large gouty deposit and found that it contained 46.7 per cent moisture and 41.7 per cent dry substance, of which there was 76.72 per cent sodium urate. This examination would quite agree with the findings of Wollaston, who was the first to state that gouty tophi are mainly composed of sodium and ammonium biurate, instead of calcium carbonate as was generally believed in his day.

#### CONCLUSIONS

1. The large majority of renal stones are composed of the oxalate of lime, sometimes the calcium salt is the only component of the stone.
2. Uric acid and the urates are found in small quantities in all renal calculi, but it is rare to find a nephritic stone composed mainly of uric acid or the urates.
3. The shape, color, consistency, etc., of a stone do not constitute criteria of its chemical composition.
4. Gouty tophi are not always composed of uric acid or the urates. In three concretions examined, a negative murexid test was invariably obtained.

These investigations were conducted in the laboratories of Prof. William J. Gies, to whom I beg to express my sincere thanks for his kind aid and suggestions throughout the undertaking. I am greatly indebted to Dr. Jacob Rosenbloom and Dr. Morris H. Kahn for their kind cooperation in procuring material for the chemical examinations.

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<sup>12</sup> Matthes, H., and Ackerman, E. *Chemisches Zentralbl.*, 1909, lxxx, 1496.

# CAUSES OF VARIATION IN THE PLATELET COUNT

EXPERIMENTAL RESULTS SHOWING THE EFFECT OF DIPHTHERIA TOXIN,  
BENZOL AND TUBERCULIN ON THE PLATELET  
COUNT IN RABBITS

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Prior to the introduction of the Wright and Kinnicutt method,<sup>1</sup> the technic for counting blood-platelets was either so laborious or so inexact that very little interest was taken in the subject by clinicians, and very few results were reported. The results reported have been at variance. Investigators have not agreed on the platelet count in health, nor on the changes which occur as a result of disease. The divergent opinions regarding the normal count are due evidently not only to the use of different counting methods, but also to a lack of unity regarding the identity of platelets. Differences of opinion respecting the pathologic changes in the count are largely due, as I shall endeavor to point out to the fact that the count may be enormously increased or decreased by the action of the same agents. It would appear that in some diseases very high and very low counts have the same cause and almost the same significance.

The normal platelet count was found between the limits of about 150,000 and 250,000 by Fusari, Muir, Deternmann and Helber, between the limits of about 200,000 and 325,000 by Hayem, Afanassieu, Van Emden and Wright and Kinnicutt, between 266,000 and 469,000 by Piatt, at an average of 500,000 by Pruss, at an average of 635,300 by Brodie and Russell, and between 730,000 and 961,500 by Kemp and Calhoun. It is evident that the last four or five observers included bodies in their counts which the former did not think were platelets. A critical review of methods for counting platelets has been made by Pratt<sup>1</sup> and Wright and Kinnicutt,<sup>2</sup> etc. The results of a series of counts made

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<sup>1</sup>Note—Results reported in brief before the Johns Hopkins Medical Society, Feb 19, 1912

<sup>2</sup>From the Medical Clinic of Professor v Romberg, Tübingen, Wurtemberg. The author desires to express his thanks to Professor Von Romberg in whose wards and laboratories this work was completed.

1 Piatt, J H. A Critical Study of the Various Methods Employed for Enumerating Blood-Platelets. Jour Am Med Assn, Dec 30, 1905

2 Wright, J H and Kinnicutt, Roger. A New Method of Counting Blood-Platelets for Clinical Purposes. Jour Am Med Assn, lvi, 1457

according to Wright and Kinnicutt's method by me on four normal individuals during a period of fourteen days, did not differ materially from those of Wright and Kinnicutt. The lowest count was 196,000, the highest 400,000, the average 262,000. The counts are given in detail in Table 9.

Pathologic variation in the platelet count has been attributed to various factors, particularly to blood regeneration, fever and malnutrition. The most constant findings have been 1 A reduced count during the febrile period of acute diseases and an increased count during convalescence. This change in the count was first observed by Hayem and was called by him a "hematoblastic crisis." It has been noted particularly in pneumonia, typhoid fever and malaria. 2 An increased count in chronic secondary anemia and in splenomyelogenous leukemia, and a reduced count in pernicious anemia and lymphocytic leukemia. 3 An increased count in chronic diseases, particularly tuberculosis. 4 A reduced count in purpura hemorrhagica. For a review of the literature on the subject the reader is referred to papers by Determann,<sup>3</sup> Helber,<sup>4</sup> Wright and Kinnicutt,<sup>1</sup> W. W. Duke,<sup>5</sup> etc.

My work was undertaken mainly for the purpose of discovering, if possible, some of the factors which give rise to variation in the platelet count. The subject was studied both clinically and experimentally. Interesting changes in the platelet count were observed in diphtheria, tuberculosis and nephritis. L. Selling<sup>6</sup> had previously observed marked changes in the count in benzol poisoning. To throw light on the findings in humans, animals were treated with varying quantities of diphtheria toxin, tuberculin and benzol and the effect of these substances on the platelet count noted.

#### METHODS

Rabbits were the animals used. It was observed in experiments carried out by me in the Hunterian Laboratory of Experimental Pathology that rabbits were better adapted to the study of blood-platelets than dogs. The changes in the count are more rapid and extreme, the bone-marrow is free from spicules of bone, and is, therefore, easier to mount for

3 Determann. Klinische Untersuchungen über Blutplättchen. Arch f klin Med, 1898, p 365.

4 Helber, E. Ueber die Zählung der Blutplättchen im Blute des Menschen und ihr Verhalten bei pathologischen Zuständen. Deutsch Arch f klin Med 1904, xxi 316.

5 Duke W W. The Pathogenesis of Purpura Hemorrhagica. THE ARCHIVES INT MED, 1912. Not yet published.

6 Selling, L. A Preliminary Report of Some Cases of Purpura Hemorrhagica Due to Benzol Poisoning. Bull Johns Hopkins Hosp, 1910, xxi, No 227, Benzol als Leukotoxin (Studien über die Degeneration und Regeneration des Blutes und der hämatopoetischen Organe) Beitr z path Anat u z allg Path 1911, li, 576.

microscopic study, and rabbits show fewer ill effects following the administration of benzol than dogs

The platelet counts were made by Wright and Kinnicutt's method,<sup>7</sup> with precautions mentioned by me<sup>7</sup> in a previous paper. Platelets in rabbits vary greatly in size, especially under the influence of diphtheria toxin and benzol. Sometimes the majority are as large as human platelets, sometimes almost as small as bacteria. Great care in the technic had to be used before constant results were obtained. Points to which especial attention was paid were scrupulous cleanliness, careful balancing of the proportions of cresyl blue and potassium cyanid used in the diluting fluid so as to give the platelets a lead blue color and avoid the precipitation of stain, and the collection of blood for the counts from hemorrhage which flowed freely from fresh cuts in the ear veins.

To those who wish to familiarize themselves with the appearance of platelets the following procedure is suggested. Allow blood to flow freely across a clean glass slide for about three minutes. Wash away the excess of blood with Wright and Kinnicutt's diluting fluid or a decalcifying solution. Cover with a cover-glass. Examine with a high dry or oil immersion lens. Such a preparation contains myriads of platelets.

The platelet count determined by me once in eighteen normal rabbits fell between 380,000 and 1,200,000. The average was 757,000. Some normal rabbits have high counts, others have low ones. Change in environment is occasionally followed by a change in the count, which may amount to as much as 50 per cent of the original count. For this reason the animals used in my experiments were kept under constant conditions for a few days before observations were started. Fluctuations were then not great enough to interfere with the value of the experimental results.

#### THE EFFECT OF DIPHTHERIA TOXIN<sup>8</sup> ON THE PLATELET COUNT

SERIES 1.—In Table 1 are recorded results showing the effect on the platelet count of doses of diphtheria toxin which caused death in rabbits in three to four days. In this series of experiments, two doses of diphtheria toxin (0.04 gm. in 2 c.c. of sterile salt solution) were given subcutaneously to three medium sized rabbits on two successive days. On the day following the second dose the animals were very quiet and sick. The ears were cold and the ear vessels so constricted that blood for the platelet count was obtained with difficulty. On the third or fourth days after the first injection the animals died.

Autopsies. The renal epithelium was degenerated in high degree. The bone-marrow was red and soft. The marrow cells had a pathologic appearance. The nuclei of a majority of the megakaryocytes were vacuolated or pyknotic.

<sup>7</sup> Duke, W. W. The Rate of Regeneration of Blood-Platelets. Jour. Exper. Med., 1911, LVI, No. 3, p. 265.

<sup>8</sup> The diphtheria toxin used in these experiments was prepared and given to me by the Hoechst Farbwerk. For this I desire to express my thanks.

TABLE 1—THE EFFECT OF LARGE DOSES OF DIPHTHERIA TOXIN ON THE PLATELET COUNT

Experiment No	24	25	26	
Weight of Rabbit	2 5 Kg	2 5 Kg	2 5 Kg	
Date	Dose of Toxin, Gm	Platelet Counts		Remarks
July—				
28		920,000	810,000	1,200,000
29	0 04	970,000	700,000	860,000
30	0 04	660,000	960,000	1,250,000
31		200,000	335,000	275,000
Aug—				
1		Found dead	Found dead	390,000
2			Found dead	Exp 26 Leuko, 20,000

SERIES II—In Table 2 are recorded results showing the effect on the platelet count of fatal doses of diphtheria toxin but smaller doses than those used in the previous series. One dose of diphtheria toxin (0 02 gm in 1 cc of sterile salt solution) was given subcutaneously to three very large rabbits. The animals were rather quiet after the third day following the inoculation but did not appear very ill. In each case death occurred rather unexpectedly.

The bone-marrow changes found in these animals at autopsy were not so marked as in the animals of the previous series. The marrow was firm and pink. The cells were less pathologic in appearance.

TABLE 2—THE EFFECT OF FATAL BUT SMALLER DOSES OF DIPHTHERIA TOXIN ON THE PLATELET COUNT

Experiment No	27	28	29	
Weight of Rabbit	4 Kg	4 Kg	3 Kg	
Date	Dose of Toxin, Gm	Platelet Counts		Remarks
June—				
2			640,000	
3	0 02	400,000	830,000	600,000
4		310,000	660,000	690,000
5				Animals lively
6		640,000	Found dead	440,000
7		640,000		480,000
8		1,400,000		Found dead
9		1,040,000		Animals quiet
10		Found dead		

SERIES III—In Table 3 are recorded results showing the effect of sublethal doses of diphtheria toxin on the platelet count. Three small doses of diphtheria toxin (0 0012 gm to 0 0024 gm in 1 to 2 cc of sterile salt solution) were given subcutaneously to three moderate-sized rabbits. The administration was discontinued as soon as the animals began to show symptoms of poisoning. These symptoms were very slight and lasted but a few days. The animals seemed more quiet than usual and the ears were cold. After two or three days the animals were again lively and strong and remained so throughout the experiment. Each animal was anemic toward the end of the experiment. On June 19 the hemoglobin (Sahli) and white count were respectively 55 per cent and 8,000 in Animal 33, 25 per cent and 16,000 in Animal 34 and 50 per cent and 5,000 in Animal 35. The majority of the leukocytes in each case were polymorphonuclear neutrophils. No blasts were seen. Animal 34 June 26 to 30 had severe purpura hemorrhagica. This experiment has been described and discussed fully in a previous paper.<sup>5</sup> Hemorrhagic diathesis in this case seems to have been the result not the cause of the reduced number of platelets. No paralysis was observed. The animals were apparently in good condition at the end of the experiment.



TABLE 3—THE EFFECT OF SUBLETHAL DOSES OF DIPHTHERIA TOXIN ON THE PLATELET COUNT

Experiment No	Weight of Rabbit	Dose of Toxin, Gm	33 2 5 Kg	34 2 5 Kg	35 2 Kg
Date			Platelet Counts		
June—					
13			530 000	430 000	1 100,000
14		0 0012	540,000	620,000	400,000
15			500 000	600 000	920,000
16		0 0018	540,000	570,000	1,090,000
17		0 0024	630,000	560 000	1,080,000
18			860,000	690,000	1,370,000
19			1,150,000	690,000	1,300,000
20			1,200 000	930,000	1,900,000
21			1,280,000	860,000	1,700,000
22			1,270,000	970,000	1 600 000
23			1,420,000	1,700,000	1,900,000
24			1,210 000	1,040,000	2,040,000
25			920,000	440 000	1,400,000
26			1 080,000	4,000	1,300 000
27			1,190,000	4,000	1,140,000
28			1,000,000	8,000	1 080,000
29			650,000	64,000	480,000
30			720,000	100,000	890,000
July—					
1			930,000	150,000	1,360 000
2			940,000	250,000	1,560,000
3			920,000	380,000	1,540,000
4			860 000	460,000	1,640 000
5			1,110,000	370,000	1,680,000
6					
7			1,160,000	550 000	2,080,000
8					
9				200,000	
10					
11			860,000	330,000	1,320,000
12					
13				230,000	

## SUMMARY OF EXPERIMENTS WITH DIPHTHERIA TOXIN

The inoculation of rabbits with diphtheria toxin in doses which proved fatal in from three to four days, was followed by a rapid fall in the platelet count to about one-third of the normal. Degeneration of the bone-marrow was found at autopsy. The nuclei of the megakaryocytes were vacuolated and picnotic. The results are shown graphically in Chart 1.

The inoculation of fatal but smaller doses of toxin gave results which were not so marked nor constant as those following the use of the larger and smaller doses. The bone-marrow changes were not so marked as those of the previous series. The results are shown graphically in Chart 2.

The inoculation of rabbits with sublethal doses of toxin was followed by, first, a rise in the count which reached, in one case, a height of 2,000,000, then a rapid fall in the count which reached in one instance the low level of 4,000, and finally, by a return of the count to normal, or by a rise above normal, which persisted for a number of days. Severe sec-

ondary anemia developed in each animal toward the end of the experiment. One animal had severe purpura hemorrhagica during the period in which the platelet count was at its lowest. This result is thought to be the effect, not the cause, of the diminished number of platelets. It has been discussed fully in a previous paper<sup>5</sup>. The results are shown graphically in Chart 3.

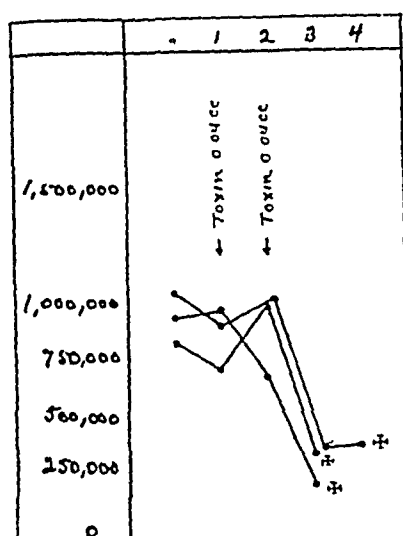


Chart 1

Chart 1—The effect of large doses of diphtheria toxin on the platelet count in three rabbits

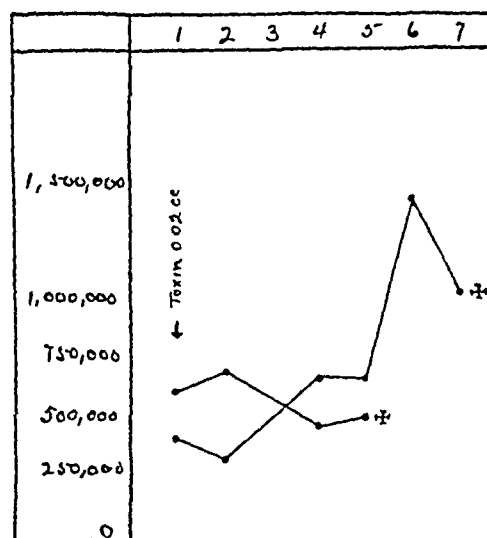


Chart 2

Chart 2—The effect of smaller but fatal doses of diphtheria toxin on the platelet count in two rabbits

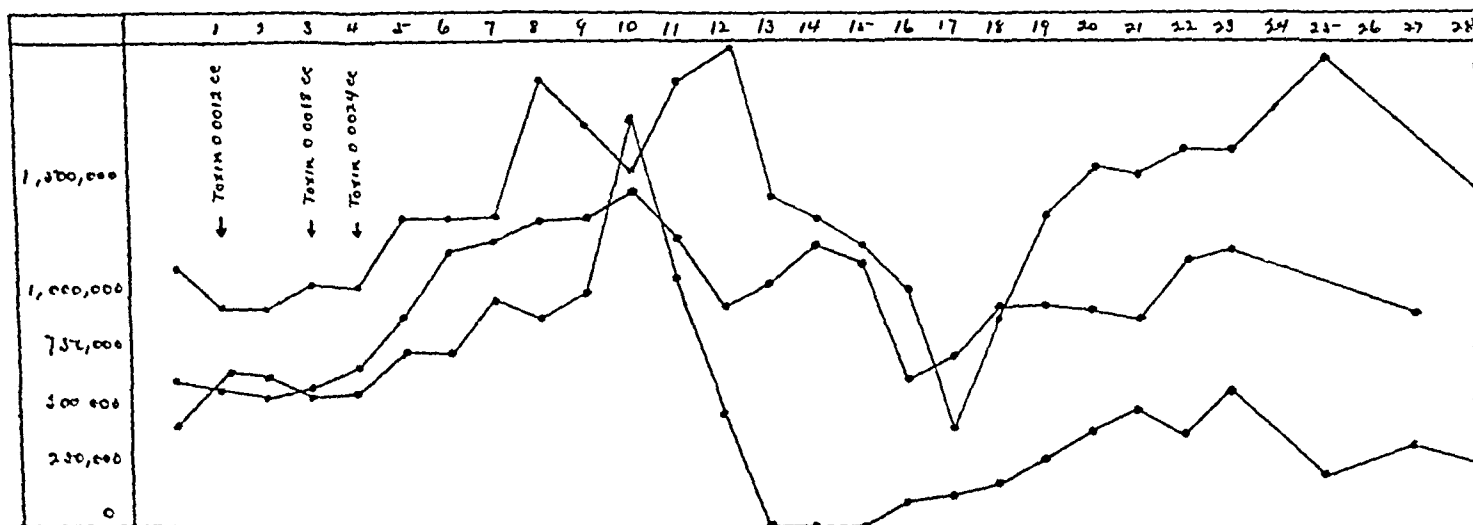


Chart 3—The effect of sublethal doses of diphtheria toxin on the platelet count in three rabbits

#### THE EFFECT OF BENZOL ON THE PLATELET COUNT<sup>9</sup>

SERIES I—In Table 4 are recorded results showing the effect on the platelet count of doses of benzol which proved fatal in about eleven days. In this series of experiments Merck's benzol was injected intramuscularly in two rather small

<sup>9</sup> The author wishes to thank Dr. L. Selling for his kind suggestions regarding the use of benzol.

rabbits for a period of five days in daily doses of 2 c c The animals at first showed no noticeable ill effects following this procedure After about the fourth day, however, it was observed that the ears were cold, that the animals were quiet and seemed weak and sick There was noted also loss of hair, loss of weight and anemia The hemoglobin was 60 per cent, Sahli, in Rabbit 23 on May 23 No abscesses developed in these rabbits In dogs treated with benzol in experiments carried out by me in the Hunterian Laboratory of Experimental Pathology there was observed in addition to the symptoms just mentioned, weak, wobbling gait, tremor, paralysis, jaundice, a mild tendency to bleed, and lipemia On the twelfth day after the first inoculation with benzol Animal 23 was found dead and Animal 22 was killed

At autopsy was found anemia and fatty degeneration of the organs and almost complete aplasia of the bone marrow Megakaryocytes were hardly to be found

TABLE 4—THE EFFECT OF FIVE 2 c c DOSES OF BENZOL ON THE PLATELET COUNT IN TWO RABBITS

Experiment No	Approx Weight of Rabbit	22		23	
Date	Dose of Benzol, c c	1 Kg	White Count	1 Kg	White Count
May—					
13	2	340,000		425,000	6,600
14	2			416,000	9,800
15	2			608,000	9,200
16	2			740,000	11,000
17	2	500,000	6,000	1,230,000	3,300
18				990,000	550
19				1,000,000	880
20		860,000	1,600	280,000	2,700
21		300,000	3,400	72,000	1,200
22		120,000	5,000	56,000	1,600
23		61,000		63,000	1,000
24		Animal killed		Found dead	

TABLE 5—THE EFFECT OF THREE 2 c c DOSES OF BENZOL ON THE PLATELET COUNT IN TWO RABBITS

Experiment No	Weight of Rabbit	36		38	
Date	Dose of Benzol, c c	1 5 Kg	Platelet Counts	1 5 Kg	Platelet Counts
July—					
24		520,000		800,000	
25		520,000		780,000	
26		730,000		880,000	
27	2 00	690,000		900,000	
28	2 00			780,000	
29					
30	2 00	820,000		680,000	
31					
Aug—					
1		910,000		810,000	
2					
3					
4		720,000		650,000	
5					
6					
7		1,220,000		1,000,000	
8					
9		1,780,000		710,000	
10					
11		1,330,000		1,380,000	
12					
13		1,320,000		1,060,000	

SERIES II—In Table 5 are recorded results showing the effect of fewer doses of benzol on the platelet count. In this series of experiments three 2 cc doses of benzol were given intramuscularly to two moderate-sized rabbits. Animals 30 and 32 of the tuberculin experiments were used. The symptoms observed were the same as those of the previous series but less severe. Subcutaneous abscesses formed in each case. The animals were in fairly good condition at the end of the experiment.

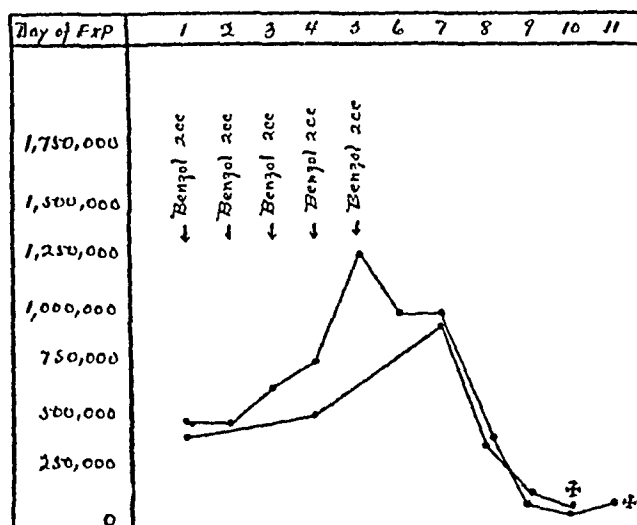


Chart 4—The effect of five 2 cc doses of benzol on the platelet count in two rabbits

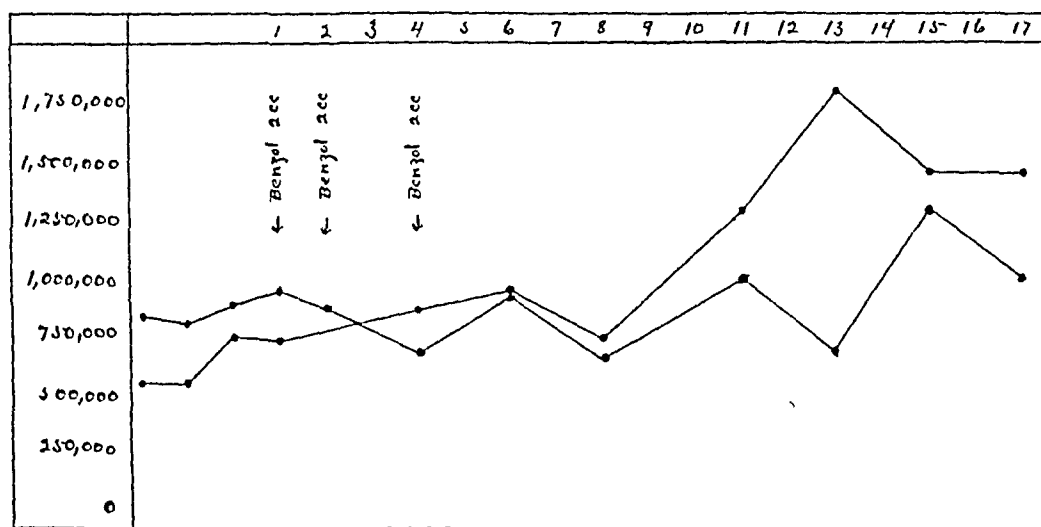


Chart 5—The effect of three 2 cc doses of benzol on the platelet count in two rabbits

#### SUMMARY OF EXPERIMENTS WITH BENZOL

The inoculation of rabbits with benzol in doses which proved fatal in about eleven days was followed by, first, a rise in the platelet count (in one case to a height of 1,230,000), then a rapid fall in the count (in one case to a level of 61,000). Severe anemia developed in each animal toward the end of the experiment.

The bone-marrow at autopsy was almost completely aplastic. Megakaryocytes could hardly be found. The results are shown graphically in Chart 4.

The inoculation of rabbits with benzol in doses which did not prove fatal within twenty days was followed by a gradual rise in the platelet count (in one case to a height of 1,780,000). The count did not fall below normal in either animal during the time of the experiment (seventeen days). The results are shown graphically in Chart 5.

#### THE EFFECT OF TUBERCULIN ON THE PLATELET COUNT

**SERIES I**—In Table 6 are recorded results showing the effect of tuberculin on the platelet count. The doses given in this series were large but were the smallest used in this work. Five doses of Koch's old tuberculin (0.1 to 0.2 gm. in 1 to 2 c.c. of a solution of dilute phenol) was given intramuscularly to three medium-sized rabbits. After a lapse of thirty-two days 0.5 gm. was given. The animals suffered no apparent ill effect from the tuberculin. They remained strong and lively throughout the experiment.

TABLE 6—THE EFFECT OF THE SMALLEST DOSES OF TUBERCULIN ON THE PLATELET COUNT IN RABBITS.

Experiment No.	Weight of Rabbit		21 2.5 Kg	22 2 Kg	23 2 Kg
Date	Dose of Tuberculin, Gm.		Platelet Counts		
May—			1,080,000	520,000	
29			1,200,000	480,000	740,000
30	0.1		900,000	400,000	660,000
31	0.1		1,730,000	590,000	720,000
June—					
1	0.1		1,300,000	610,000	960,000
2	0.15		1,500,000	730,000	940,000
3	0.2		1,370,000	720,000	800,000
4			1,000,000	530,000	710,000
5					
6			920,000	600,000	600,000
7					
8					
9			1,140,000		720,000
10					
11					
12					
13				840,000	570,000
July—					
5	0.5			1,100,000	650,000
6				640,000	700,000
7				810,000	800,000
8					
9				740,000	760,000
10					
11				880,000	660,000

**SERIES II**—In Table 7 are recorded results showing the effect of larger doses of tuberculin on the platelet count. Tuberculin gm. 1.0 undiluted was given intramuscularly to three rather small rabbits. On the fifth day after the inoculation the animals seemed a little sick and quiet. After two or three days they seemed lively and strong again and remained so throughout the experiment.

TABLE 7—THE EFFECT OF LARGER DOSES OF TUBERCULIN ON THE PLATELET COUNT IN RABBITS

Experiment No	Weight of Rabbit	Dose of Tuberculin, Gm	30 1 5 Kg	31 1 5 Kg	32 1 5 Kg
Date			Platelet Counts		
June—				440,000	340,000
14		1 0	590,000	420,000	380,000
15			650,000	410,000	390,000
16			520,000	405,000	420,000
17			720,000	620,000	1,080,000
18		.	900,000	580,000	830,000
19				.	
20			1,200,000	840,000	960,000
21			600,000	770,000	800,000
22			550,000	570,000	800,000
23			630,000	500,000	800,000
24			520,000	470,000	800,000
25			520,000	510,000	780,000
26			730,000	580,000	880,000
27			690 000	430,000	900,000

SERIES III—In Table 8 are recorded results showing the effect of the largest doses of tuberculin on the platelet count. Gm 3 0 of tuberculin undiluted was given intramuscularly to three small, young rabbits. The dose in this series was gm 3 0 per kilo of weight. For one or two days after the inoculation the animals seemed quiet and sick but on the third day were again lively. After a period of one week, there was noticeable loss of weight and at the end of the experiment emaciation was quite marked. Ulceration developed on the hind legs of each animal at the end of the first week and finally the legs seemed almost to dry up. The ears also withered toward the end of the experiment and blood could be obtained only by cutting the largest vessels. Severe anemia developed in each animal toward the end of the experiment.

TABLE 8—THE EFFECT OF LARGE DOSES OF TUBERCULIN (3 GM PER KILO OF WEIGHT) ON THE PLATELET COUNT IN RABBITS

Experiment No	Weight of Rabbit	Dose of Tuberculin, Gm	36 1 Kg	37 1 Kg	38 1 Kg
Date			Platelet Counts		
July—					
22			980,000	360,000	1,200,000
23		3 0	830 000	790,000	1,320,000
24			860 000	650,000	880,000
25			730,000	800,000	1,030 000
26			1,290 000	780,000	1,113,000
27			1,100 000	1 070,000	1,360 000
28					
29			910 000	810,000	
30					
31					
Aug—					
1			900 000	600 000	1,900,000
2					
3			1 880 000	530 000	1 920 000
4			2 200 000	820 000	2 320,000
5			1 720 000	830 000	1 600 000
6			Found dead		
7				740,000	Found dead

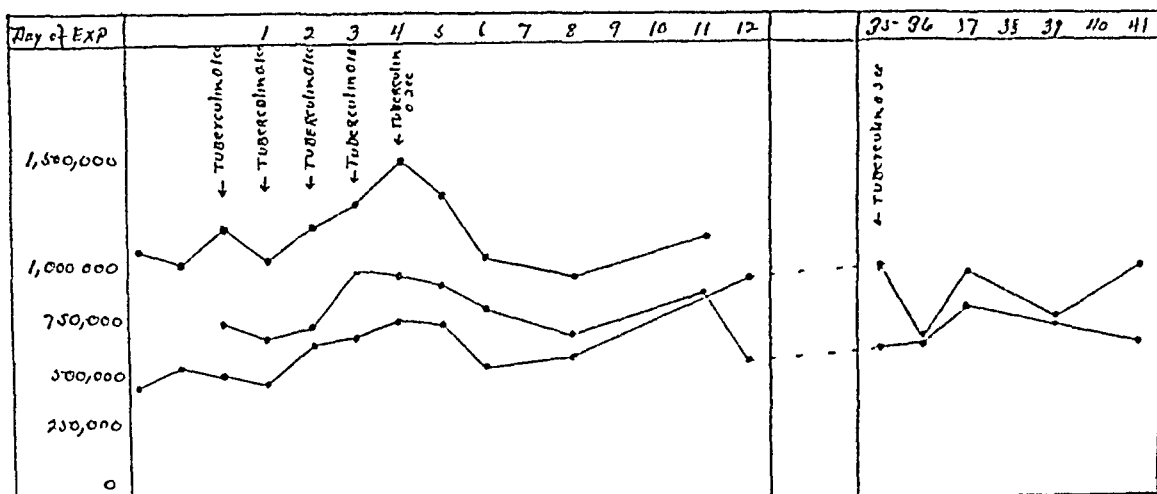


Chart 6—The effect of tuberculin in doses of about gm 0.25 per kilo of weight on the platelet count of three rabbits. Gm 0.6 was given in divided doses during a period of five days. After an interval of thirty-two days a second dose of gm 0.5 was used.

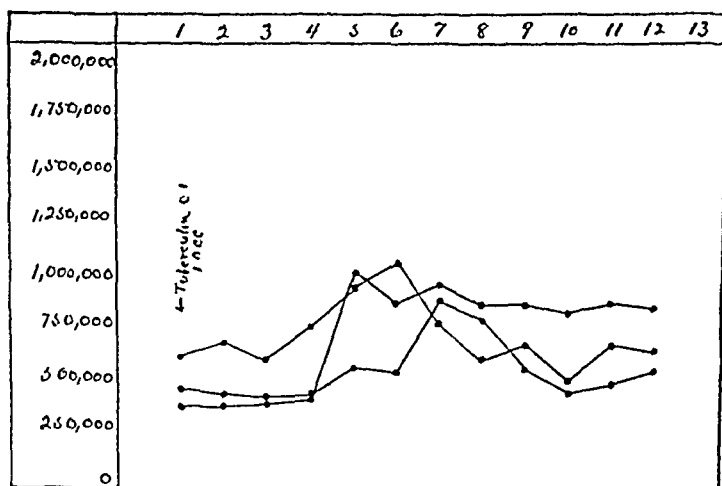


Chart 7—The effect of tuberculin gm 0.7 per kilo of weight on the platelet count of three rabbits.

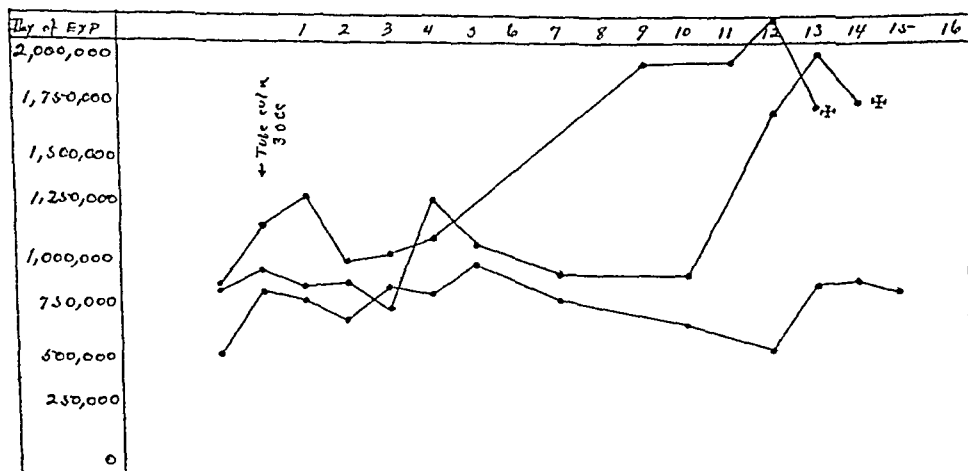


Chart 8—The effect of tuberculin gm 3.0 per kilo of weight on the platelet count of three rabbits.

## SUMMARY OF EXPERIMENTS WITH TUBERCULIN

The inoculation of animals with large doses of tuberculin was followed by a rise in the platelet count in nearly every instance. The change in the counts was in general not so marked as that observed in the previous experiments. The most striking result followed the use of the largest doses (3 gm per kilo of weight), in two of which experiments the count reached a height of more than 2,000,000. The count did not fall below normal in a single instance. Severe anemia developed in the animals receiving the largest doses. The results are shown graphically in Charts 6, 7 and 8.

## DISCUSSION OF RESULTS

In a previous paper it was suggested by me that platelets were probably very short-lived bodies, or what amounts to the same thing, that platelets either disintegrate or are utilized and regenerated in enormous numbers daily. This view, while not directly proved, harmonizes well with facts as known at present. The facts are as follows.

1 The platelet count under normal conditions is relatively more variable than the red count. A comparison between the two is well shown in Table 9, in which are recorded a series of platelet counts made by me in four normal individuals, and in Table 10, in which are recorded series of red counts made by Professor Burker<sup>10</sup>

TABLE 9 —PLATELET COUNTS IN FOUR NORMAL INDIVIDUALS

Date	1	2	3	4
May—				
9	275,000	295,000	290,000	315,000
10				
11				
12	220,000	300,000	280,000	240,000
13				
14		280,000		
15		270,000		190,000
16	225,000	300,000	300,000	
17				220,000
18		240,000		190,000
19	230,000		350,000	
20	225,000		275,000	
21		260,000		
22	196,000		400,000	
23	220,000			
24	240,000		250,000	
Highest count	275,000	300,000	400,000	315,000
Lowest count	196,000	240,000	250,000	190,000
Average	224,000	264,000	306,000	231,000

<sup>10</sup> K. Bürker. Ueber weitere Verbesserungen der Methode zur Zählung roter Blutkörperchen nebst einigen Zahlresultaten. Pflügers Archiv f. ges. Physiol., 1911 cxlii, 337.



TABLE 10—THE RED COUNT IN NORMAL PERSONS AS OBSERVED BY PROFESSOR BURKIN

Period I*	Period II	Period III
5,250,000	5,470,000	5,420,000
5,370,000	5,270,000	5,320,000
5,320,000	5,280,000	5,150,000
5,330,000	5,370,000	5,360,000
5,200,000	5,430,000	5,220,000
5,170,000	5,400,000	5,410,000
5,120,000	5,250,000	5,430,000

Highest count 5,470,000    Lowest count 5,120,000    Average 5,320,000

\*The counts were made on successive days in the same individual at three periods about five weeks apart

2 The platelet count when pathologically increased or decreased is more variable than the count under normal conditions. Daily fluctuations may be as great as the normal count. Results recorded in Table 11 obtained from patients with advanced phthisis (A) and severe nephritis (B), both observed by me in the clinic of Professor Romberg, are given as examples. The red count is never subject to such great and rapid changes as these.

TABLE 11—PLATELET COUNTS IN A PATIENT WITH (A) ADVANCED PHTHISIS, (B) SEVERE NEPHRITIS

A		B	
Date	Platelet Counts	Date	Platelet Counts
June—		May—	
14	210,000	9	1,260,000
18	4,000	10	1,120,000
20	10,000	12	760,000
21	1,000*	16	575,000
22	110,000	19	535,000
23	210,000	24	510,000
24	295,000	25	540,000
25	330,000	26	640,000
26	385,000	28	760,000
27	520,000	29	800,000
28	550,000	June—	
30	720,000	1	786,000
July—		8	560,000
1	720,000	15	400,000
7	640,000	16	350,000
12	400,000	25	1,400,000
17	500,000	July—	
		3	900,000
		5	500,000

3 It was demonstrated by me in the Hunterian Laboratory of Experimental Pathology and in the pathological laboratory of the University of Kansas that the total number of platelets in the blood of dogs can be regenerated within a period of from three to five days. To prove this dogs were bled in amounts of 200 to 250 c c. The blood was defibrinated and re injected intravenously. This process was repeated frequently at short intervals, so that finally the fibrinogen of the circulating blood was

reduced to a trace. Platelets are removed from the blood by defibrination. The platelet count of these animals was therefore also reduced to a minimum. Counts were made at short intervals after the operation, and the rate at which it returned to normal was observed. In each of the five experiments the count reached normal within from three to five days. The results obtained in two of these experiments are shown graphically in Chart 9. As compared with the rate of regeneration of red cells in a condition somewhat analogous (secondary anemia), that of the platelets is much more rapid. The regeneration of the total number of platelets in the blood is a matter of days, while the regeneration of about 50 per cent of the red cells is a matter of weeks. The relatively slow rate at which red cells are regenerated in dogs when their number is reduced by bleeding and injection of salt solution, is shown in Chart 10, in which are recorded graphically the results obtained by D<sup>r</sup> P M Dawson<sup>11</sup>.

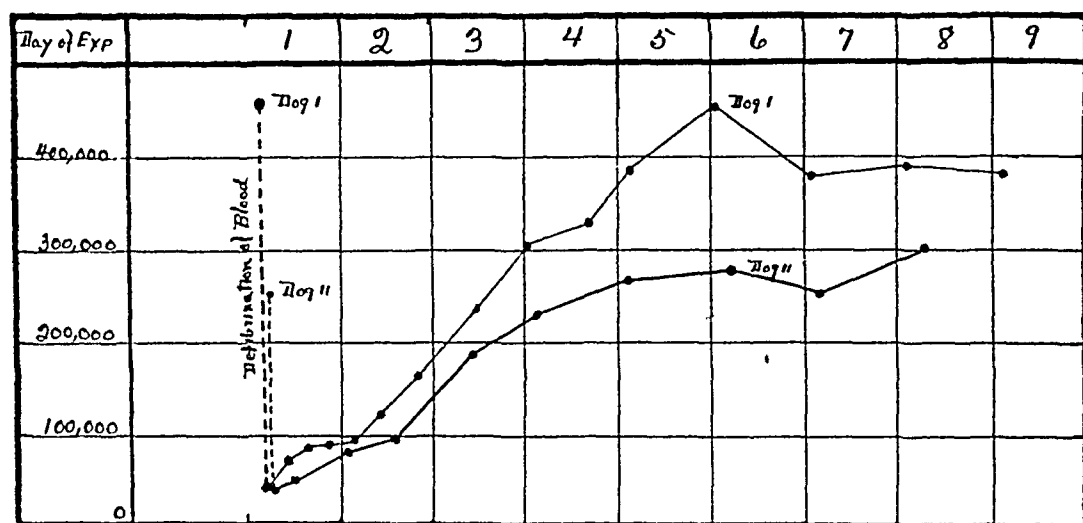


Chart 9—About 90 per cent of the platelets in two dogs were removed from the circulation by withdrawing, defibrinating and reinjecting 200 cc amounts of blood six to ten times during a period of four hours. The chart shows the rapid rate at which the count rose after it was thus reduced. It reached normal in one animal on the fourth day, in the other on the fifth.

4. In a previous paper<sup>12</sup> I reported results obtained from the study of two patients observed in the Massachusetts General Hospital, who had hemorrhagic disease. Both patients had very low platelet counts (3,000 to 20,000). Following direct transfusion of blood, the counts were found to be 123,000 and 89,000, respectively. The increase in the count was due evidently to the introduction of the donor's platelets into the patient's circulation. The counts fell again rapidly after transfusion and within three days reached their previous low level. The red counts, also increased by the transfusion, remained high for a period of weeks.

<sup>11</sup> Dawson P M. Effects of Venous Hemorrhage and Intravenous Infusion in Dogs. *Am Jour Physiol* 1900 iv No 1.

<sup>12</sup> Duke W W. The Relation of Blood-Platelets to Hemorrhagic Disease. *Bour Am Med Assn* 1910 iv, 1185.

The following experiment was performed by me in the Hunterian Laboratory of Experimental Pathology. A dog was treated for six days with intramuscular injections of benzol. The platelet count at the beginning of the experiment was 284,000. Three days after the last dose of benzol the count was 26,500. The animal was then bled and transfused by the Cule method<sup>13</sup>. An animal of the same breed was used as donor. Immediately after transfusion the platelet count was 179,000. Twenty-four hours later it had fallen to 110,000. The red count was also increased by transfusion and remained high. This experiment was, of course, incomplete. It is reported simply in confirmation of the results obtained in humans.

The above facts admit several possible interpretations. At present the following seems to me the most logical. Future work may prove it erroneous.

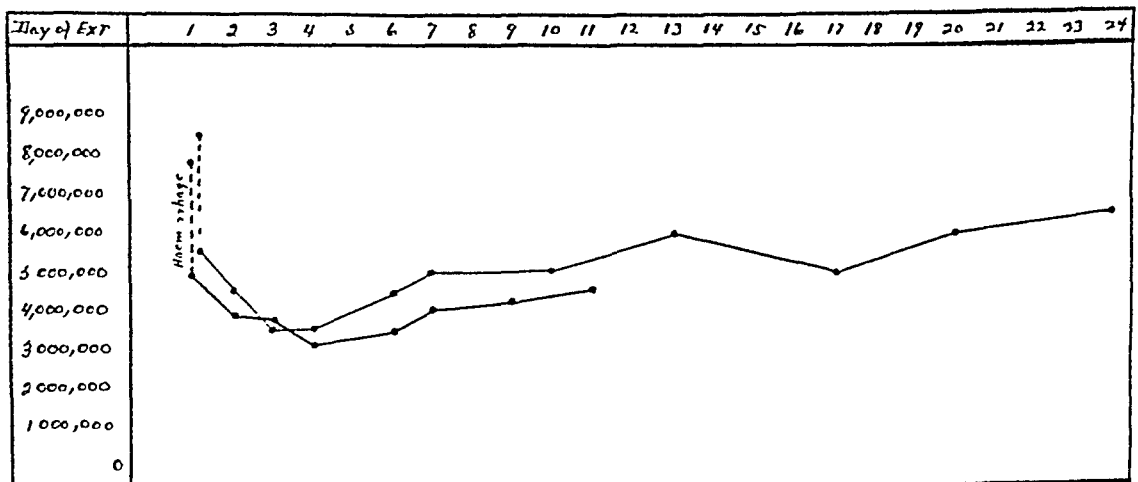


Chart 10—Results of Dr P M Dawson. The red count in two dogs was reduced by withdrawing a large amount of blood and replacing it with salt solution. The chart shows the relatively slow rate at which the red counts rose after they were thus reduced. They did not reach normal in three weeks. The conditions of these experiments and of those of Chart 9 would seem to be somewhat analogous.

Let us assume that the average length of life of platelets in a given individual is four days. If the platelet count were 400,000, we could suppose that in this individual about 100,000 platelets disintegrated and were regenerated daily. If now the rate of formation of platelets were suddenly doubled through the action of some stimulating agent, the count would rise rapidly to 800,000, and if made fivefold would rise in a few days to 2,000,000, that is, if the platelets formed under the new conditions lived out the same life cycle as those formed under normal conditions. If now the increase in the count to 2,000,000 were brought about by an agent which first stimulated, then paralyzed the production

<sup>13</sup> The transfusion was carried out by Dr W D Gatch, to whom I desire to express my thanks.

of platelets, a fall in the count at an average rate of 500,000 a day would take place the day the paralysis was complete. If the paralysis occurred suddenly the count would fall from 2,000,000 to 0 within a period of four days. The fundamental point in this assumption is that the life cycle of the platelet is short, that is, that platelets are destroyed and regenerated in enormous numbers daily. Let us see how it conforms to actual fact.

It would harmonize with the fact that the platelet count is less constant than the red count. If the daily disintegration of platelets is 25 per cent of the total number in the blood, one would expect that the count would be less constant than the red count where the daily disintegration is relatively much less in amount. Likewise, it would harmonize with the fact that platelets can increase or decrease in number so rapidly in various pathologic and experimental conditions. A pathologic rise or fall in the count at the rates observed (often 500,000 per day) would not seem remarkably great if the normal rate of formation were 100,000 per day. If, however, the normal rate of formation were say 20,000 per day, a pathologic rise or fall such as that mentioned would seem very large (twenty-five times the normal rate). If the latter were true, we would have to assume that fluctuations observed in my experiments were the effects of agents highly stimulating or destructive. This is of course a possibility, but does not harmonize well with all our facts. The same reasoning may be applied in accounting for the fact that the platelets introduced into the circulation of the patients with hemorrhagic disease to which I referred, disappeared so rapidly. In this case we had normal platelets in plasma, which may or may not have been destructive to them. If the life cycle of the platelet is normally short, the rapid disappearance was a more or less physiologic incident; if the life cycle is normally long, the platelets must have been destroyed prematurely.

While the assumption of either a short or long life cycle for platelets may be consistent with the results already mentioned, that of a normally long life would not account well for the fact that platelets can be regenerated so rapidly after their removal from the circulation by repeated defibrination of the blood. Such a view would suppose that the experimental condition led to a rate of generation of platelets which was much greater than the normal. This is, however, possible. It may be that a lack of platelets or some other condition in the experiments was a powerful stimulus to platelet generation. It may be repeated, however, that analogous stimulation to the formation of erythrocytes (the lack of red cells in secondary anemia) causes no such rapid rise in the red count.

While I believe that platelets are generated and destroyed at a rapid rate under normal conditions, and that this is a factor which must be constantly borne in mind when one interprets the meaning of pathologic variation in the platelet count, I do not deny that other factors may play a part. For example, in the experiments with large doses of benzol and

diphtheria toxin, it was noted that the platelets became smaller and smaller as the count rose. It is not impossible that platelets in the blood-stream were broken up into smaller pieces by the action of these agents and that this contributed to the rapid rise in the count. It is also possible that these small platelets observed in the experimental conditions disintegrated more rapidly than normal platelets, and that this contributed to the rapid fall in the counts which followed. It is possible that platelets in the circulating blood are destroyed by benzol and diphtheria toxin, and that this gave rise in part to the fall in the counts noted in some of the experiments. It is hard to believe, however, that such occurred in the experiments with diphtheria toxin of Series III. The count did not begin to fall in these animals until ten days or more after the administration of the last dose of toxin, and at that time the animals had apparently recovered from the direct ill effects of the poison. One other possibility must also be mentioned. It is well known that after animals have been treated with a foreign serum or peptone, platelets have a tendency to clump and form capillary plugs. The result is that the platelet count may be considerably reduced. It is possible that a clumping of the platelets occurred in some of my animals and diminished the number in the circulating blood. To me it does not seem probable, however. First, the platelets were always evenly distributed when the blood was mixed with Wright and Kinnicut's solution. Second, the fact that the animals developed anemia and had pathologic changes in the bone-marrow suggests another cause for the fall in the counts. Further experiment is necessary, however, before this point can be definitely settled.

The experiments, I believe, can best be interpreted as follows:

Diphtheria toxin in large doses is immediately poisonous to the bone marrow—possibly also to the platelets in the blood stream—and causes an immediate fall in the platelet count.

Benzol, as administered in the experiments of Series I (that is in large doses), and diphtheria toxin as administered in the experiments of Series III (that is, in sublethal doses), act first as stimulants and then as poisons to the progenitors of platelets, thus causing first a rise and then a fall in the platelet count. It may be that platelets themselves are also affected by these agents and that this factor contributes to the change in the counts. It is believed that the rapidity of the changes can be accounted for best by assuming that platelets normally are short lived bodies.

Benzol, as administered in the experiments of Series II (that is, in smaller doses), and tuberculin act for a period of ten days or more as stimulants to the formation of platelets. No evidence of a poisonous effect during this period was observed in my experiments. In two of the experiments with diphtheria toxin of Series III, the irritating effect of the poison was greater and more lasting than the poisonous effect. The actual result was an increase in the platelet counts. It seems likely that still smaller doses would produce an irritant effect only.

The experimental work gives us a clearer conception of some of the processes which cause variation of the platelet count and enables us to understand better the findings in humans. In the Children's Hospital of Professor Escheich I made a number of platelet counts on patients with diphtheria. As a rule, the count was reduced during the febrile period of the disease (lowest count 3,000) and increased during convalescence (highest count 750,000). The opposite change, however, was also observed, that is, an increase in the count during the febrile period and a reduction in the count after the clearing of the membrane. The counts then followed the phases of Hayem's crisis as a rule, but the reverse of this also occurred. Examination of Chart 11 in which is recorded graphically the effect of varying doses of diphtheria toxin on the platelet count shows strikingly that under the influence of diphtheria toxin the platelet count may range at almost any level at almost any time. The behavior

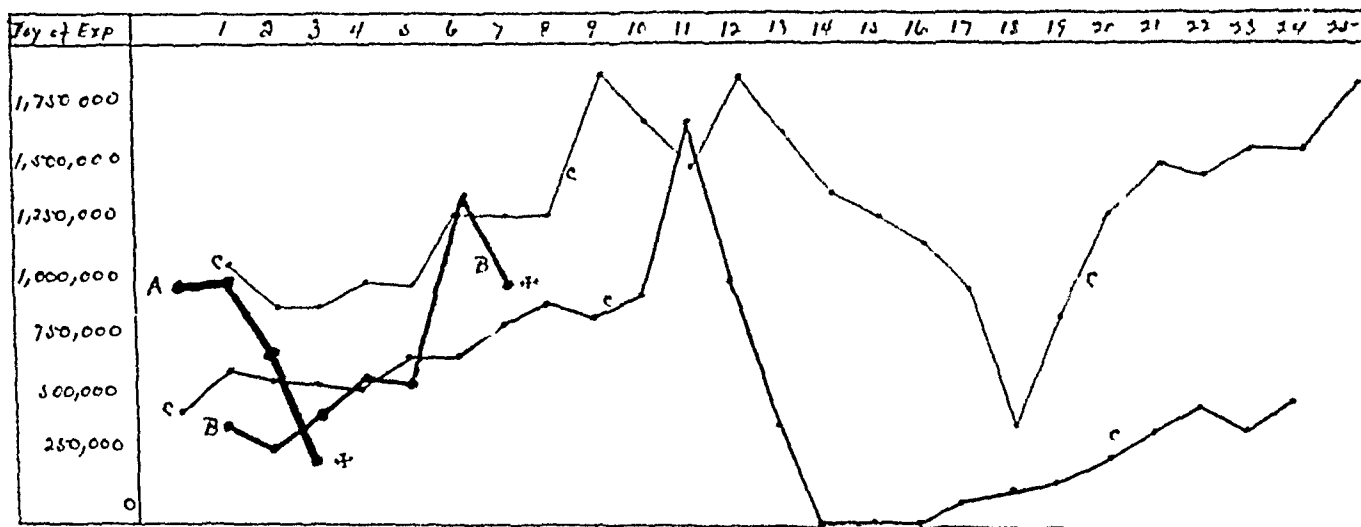


Chart 11—The effect of diphtheria toxin in varying dosage on the platelet count in rabbits (A) Largest dose (B) Smaller but fatal doses (C) Sublethal doses

of the count depends on the amount of the toxin administered, and possibly also to a slight extent on the individual resistance of the animal. It suggests that Hayem's crisis in humans with diphtheria is the result of a large amount of toxin, and that the reverse change is the effect of a smaller amount. Low counts would indicate a greater toxemia than high counts, and low counts early in the disease a more severe case than low counts late in the disease.

I made a number of platelet counts on patients with phthisis and nephritis in the medical clinic of Professor Romberg. The platelet count in patients with advanced phthisis was as a rule increased, occasionally very much so (highest count 1,000,000). In two cases it was greatly reduced for a short time (in one case to 55,000, in another to less than 1,000). In patients with severe nephritis and urinary retention the

count was increased as a rule—occasionally very much increased (highest count 1,260,000) In no case was it reduced Pratt,<sup>14</sup> however, has reported a case of nephritis in which the platelet count descended to 9,000, and Determann<sup>3</sup> an instance in which the count was 90,000 It would appear that the platelet count may be very much increased or very much decreased in phthisis and nephritis In diphtheria, the count is increased and decreased by one and the same agent, diphtheria toxin It

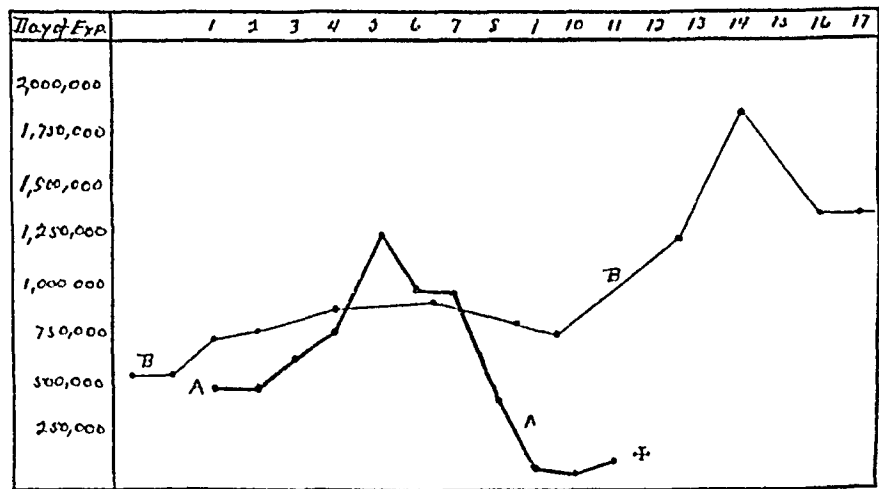


Chart 12—The effect of benzol in varying dosage on the platelet count in rabbits (A) Dose fatal in eleven days (B) Smaller dose

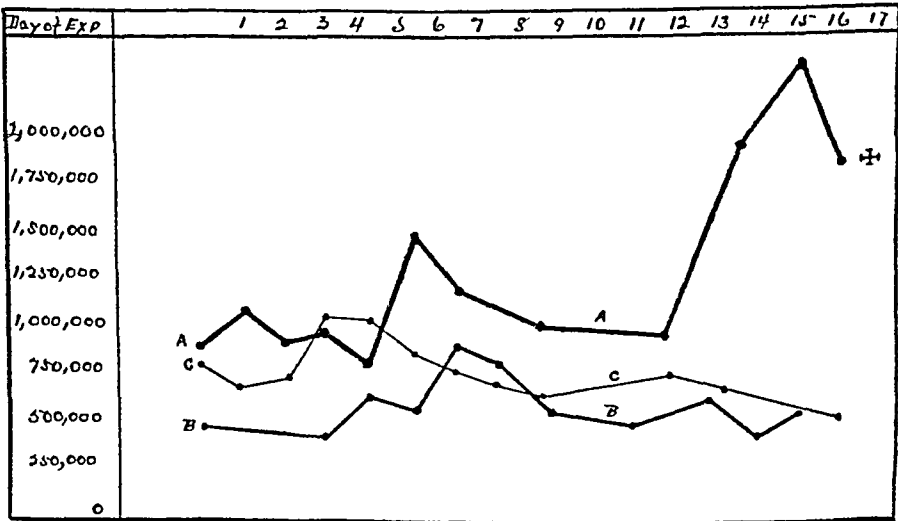


Chart 13—The effect of tuberculin in varying dosage on the platelet count in rabbits (A) Largest dose (B) Smaller dose (C) Smallest dose

seems that the high and the low counts of phthisis and possibly also of nephritis and of many other diseases may be likewise the effect of varying quantities of one and the same agent High counts would seem to be the effect of doses which act as irritants, low counts the effect of poisonous

14 Pratt, J H A System of Medicine Osler and McCrae, vol iv, p 681

*doses It would appear from the data at hand that where the agent effecting the count is a mild one (such as tuberculin and presumably also the platelet poisons of nephritis or phthisis) the count is increased as a rule, and in rare cases reduced Where the agent is a stronger one (such as benzol or diphtheria toxin) the counts are more quickly and markedly altered, and low counts (the effect of poisonous doses) are more frequent*

#### SUMMARY AND CONCLUSIONS

The inoculation of rabbits with doses of diphtheria toxin which proved fatal in three days was followed by an immediate fall in the platelet count to about one-third of the normal Severe degeneration of the bone-marrow was found at autopsy The nuclei of a majority of the megakaryocytes were vacuolated or pyknotic

The inoculation of rabbits with sublethal doses of diphtheria toxin was followed by, first, a rapid rise in the platelet count which reached in one instance a height of 2,040,000, then a rapid fall in the count which reached in one instance the low level of 4,000, and finally by a rise in the count to normal or by a rise above the normal which persisted for a number of days The animals developed severe anemia toward the end of the experiment

The inoculation of rabbits with five 2 c c doses of benzol was followed by, first, a rapid rise in the platelet count in one instance to a height of 1,230,000, then a rapid fall in the count in one instance to 61,000. The animals developed severe anemia The bone marrow at autopsy was almost completely aplastic Megakaryocytes were hardly to be found

The inoculation of rabbits with three 2 c c doses of benzol was followed by a gradual rise in the platelet count, in one instance to a height of 1,780,000 The count did not fall below normal during the period in which observations were made

The inoculation of rabbits with tuberculin was followed in nearly every instance by a rise in the platelet count The most striking results followed the use of the largest doses (gm 3 per kilo of weight) In two instances the count exceeded 2,000,000 In no case did the count fall below normal Severe anemia developed in the animals receiving the largest doses

These data it is thought, admit the following interpretation Diphtheria toxin in large doses is immediately poisonous to the bone marrow—possibly also to platelets themselves—and causes an immediate fall in the platelet count

Benzol in large doses and diphtheria toxin in sublethal doses, act first as stimulants, and then as poisons to the platelet-forming organs and cause thus first a rise and later a fall in the platelet count It is possible that the platelets themselves are also affected by these agents, and that this contributes to the change in the counts



Tuberculin in large doses, benzol in small doses and possibly also diphtheria toxin in very small doses, act for a certain period of time only as stimulants to the progenitors of platelets and cause only a rise in the platelet count

It is believed that both the high counts and the low platelet counts observed by me in humans with diphtheria are caused by the action of varying amounts of one and the same agent—diphtheria toxin. Low platelet counts in this disease would indicate a more severe toxemia than high counts, and low counts early in the disease a more severe case than low counts late in the disease. This reasoning it is believed may apply to other diseases also, and would seem to account for the occurrence of high platelet counts and low platelet counts in the same pathologic conditions

It has been suggested by several observers that a poverty of the blood in platelets plays a rôle in the pathogenesis of purpura hemorrhagica. The work reported here supports this view. Purpura hemorrhagica of a certain type was observed in every instance (human and experimental) in which the platelet count descended to a certain low level.

The view expressed by me in a previous paper that platelets were probably very short-lived bodies harmonizes with the results reported here and it is believed accounts for the fact that the platelet count can rise and fall with such rapidity.

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## THE EFFECTS OF EXPERIMENTAL CHRONIC PASSIVE CONGESTION ON RENAL FUNCTION\*

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BALTIMORE

By experimental methods, the production of varying grades of chronic passive congestion of the kidney has been attempted in order to determine its effect on the urinary and clinical findings, on the excretory capacity of the kidney as revealed by certain functional studies and on the histological structure of the kidney.

In every cardiorenal case which he encounters the physician confronts problems which he is called on to solve. Is the heart or kidney chiefly involved in this case? Which is more responsible for the clinical picture here exhibited? Do permanent and irreparable organic changes exist in the kidneys which preclude the hope of reestablishing a condition of relatively good health, or will the decreased renal function return to normal with the improvement in the cardiovascular system consequent on the enforced confinement to bed? Can chronic passive congestion alone be responsible for the clinical findings? Shall the treatment be directed chiefly to the heart or to the kidneys? Can chronic passive congestion itself interfere to any considerable degree with the excreting capacity of the kidney or can it *per se* institute pathological processes which result in organic and irreparable changes which decrease the capability of the kidney to carry on its work?

By correlating the data obtained from this study with those obtained by utilizing clinically these identical functional tests in a rather extensive series of cardiac, cardiorenal and renal cases, we have attempted to devise some means whereby these problems can be successfully attacked

### HISTORICAL

The effect of partial or complete obstruction to the venous return from the kidney on the urinary picture and the histology of the kidney has been already investigated. Robinson<sup>1</sup> (1843) showed that complete or partial tying off of the renal vein resulted in the appearance of albumin

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\*From the Pharmacological Laboratory of the Johns Hopkins University and the Medical and Genito-Urinary Clinics of the Johns Hopkins Hospital

<sup>1</sup> Robinson Med Chir Tr, 1843, xxvi, 51

or blood, or both, in the urine, and in the enlargement of the kidney itself. He also performed a one-sided nephrectomy and showed that albumin sometimes appeared in the urine following such an operation, but that by tying the aorta below the level of the renal arteries, together with the above mentioned operation, the appearance of albumin in the urine was more likely to occur. None of Robinson's animals lived more than four and one-half days.

Robinson's work, as well as that of several other investigators, Meyer<sup>2</sup> (1844), Frerichs<sup>3</sup> (1851), Goll<sup>4</sup> (1854), Ludwig<sup>5</sup> (1856), Munk<sup>6</sup> (1864), Erythropel<sup>7</sup> (1865), Stockvis<sup>8</sup> (1867), Weissgerber and Perls<sup>9</sup> (1877), Litten<sup>10</sup> (1879), Posner<sup>11</sup> (1880), Cohnheim<sup>12</sup> (1882), and Heidenham<sup>13</sup> (1883), has unquestionably established three facts in relation to complete or partial obstruction of the venous return from the kidney for periods varying from hours to a few days:

1 Albuminuria is produced

2 Hematuria results, particularly if the lumen of the vein be greatly narrowed

3 Numerous epithelial cells, singly, in groups, or as epithelial casts, appear in the urine

There is not the same unity of opinion concerning the occurrence of casts in the urine under these conditions, Munk, for example, stating that fibrous and gelatinous casts (*Faserstoff und Gallert*) are never encountered except where nephritis coexists. Burkart<sup>14</sup> also states that following ligation of the renal vein he obtained infarction of the kidney, but no casts in the urine. The consensus of opinion, however, is that casts do occur when the venous return is interfered with, having been described by Frerichs, Erythropel, Weissgerber and Perls, Runeberg<sup>15</sup> and Litten.

Another phase, the effect of obstruction of venous outflow on the quantity of urine excreted, has also been investigated. Paneth<sup>16</sup> (1886) in cleverly devised experiments on anesthetized animals in which known weights were allowed to make traction on a thread, the loop of which

2 Meyer Arch f phys Heilkunde, 1844, III, 116

3 Frerichs Die Bright'sche Nierenkrankheit und deren Behandlung, 1851, p 276

4 Goll Ztschr f rat Med, IV, 78

5 Ludwig Physiologie, II, 416

6 Munk Berl klin Wchnschr, 1864, I, 333

7 Erythropel Ztschr f rat Med, 1865, XXIV, 217

8 Stockvis J de méd, chir et pharm, 1867, LV, 22

9 Weissgerber and Perls Arch f Pathol u Pharmakol, 1877, VI, 116

10 Litten Untersuchungen über den hemorrhagischen Infarkt, 1879, p 3

11 Posner Virchow's Arch f path Anat, 1880, LXXIX, 311

12 Cohnheim Allg Pathol, 1882, II, 314

13 Heidenham Herrmann's Handbuch der Physiologie, 1883, V, 324

14 Burkart Die Harnzylinder, Berlin, 1874, p 46

15 Runeberg Deutsch Arch f klin Med, 1879, XXIII, 225

16 Paneth Pflüger's Arch f d ges Physiol, 1886, XXXIX, 515

was placed about the inferior vena cava above the entrance of the renal vein, or about the renal vein itself, showed that venous congestion *always* caused a decrease in the urinary output. Even the mildest grades of congestion were never associated with a normal or increased amount of urine. Similar conclusions had been drawn by Munk<sup>6</sup> (1864)

Schwarz<sup>17</sup> (1900) states that partial obstruction of the renal vein of one side resulted in a relative polyuria on that side. This he claimed could be obtained with more certainty when the blood was first defibrinated.

De Souza<sup>18</sup> (1900) repeated this work with exactly opposite results even when the blood was defibrinated. He sharply criticized the work of Schwarz, pointing out that the flow of urine from either side, in Schwarz's experiments, was exceedingly small. He concluded that any interference with the return flow of blood from the kidney resulted in lessened urinary output.

Ignatowski<sup>19</sup> (1905) determined the effect on the renal function of ligating one renal vein, the other kidney being left untouched. He showed that the urine for the next twenty-four hours was scanty in amount, poor in chlorid and in urea, contained albumin and blood. He later tied the remaining renal vein, death occurring within a few days.

The work of these various investigators has dealt essentially with the immediate effect (hours to four days) of partial or complete obstruction of the venous return from the kidney on the amount of urine, the presence of albumin, blood and casts in it, and on the histological picture.

The problems with which we deal are, the effects of varying grades of permanent chronic passive congestion (partial obstruction to venous return) on the urinary picture, on the functional capacity of the kidney as revealed by functional studies, on the kidney histologically, and on the general condition of the organism elsewhere.

#### METHODS

The method utilized for the production of chronic passive congestion of the kidney consisted briefly of the application of constricting bands about the renal veins or about the vena cava above the entrance of the renal veins. The bands were obtained by cutting sections approximately 1 cm. in length from ordinary Coudé catheters which were sterilized by boiling for a period of two or three minutes.

The dog's abdomen was opened aseptically. The vessel about which the band was to be placed was isolated and thoroughly freed from the surrounding tissue. The section of catheter was slit longitudinally, opened, flattened out, and grasped between the blades of an artery forceps in such a manner as to prevent it from curling back into its original shape.

17 Schwarz. Arch f Physiol u Pathol, 1900, xliii, 15

18 De Souza. Jour Physiol, 1900, xxvi, 139

19 Ignatowski. Compt rend Soc de biol, 1905, lviii, 130

The band was slipped under the isolated vessel and grasped on the other side with forceps. By careful manipulation it was allowed to curl back into its original shape, enclosing the vessel within its lumen. Heavy silk ligatures were then tied about it, in the center and at either end, holding it firmly in place. The degree of congestion produced was controlled by the caliber of the band utilized, by one-sided nephrectomy, and by ligating or leaving untouched the vessels concerned in the collateral circulation of the kidney. The dog was then allowed to recover from the anesthesia and was placed in an appropriate metabolism cage for immediate observation.

After a series of functional studies the animal was turned loose until such a time as another series was wanted. Repeated observations at periods of days or weeks were made on the urine and on the renal functional capacity. Finally the dogs were killed and the kidneys studied from a pathological point of view.

We have in this manner attempted to create conditions simulating as nearly as possible those existing in cases of cardiac decompensation. In clinical cases there is stasis which undoubtedly interferes with the free flow of blood from the kidney. Since the heart action in cases of decompensation is weakened, there must exist a disproportion between the driving force on the arterial side and the outflow on the venous side. And while our experiments have been conducted on animals with normal hearts, the constriction of the vein leads here also to a disproportion between the inflow and the outflow. Therefore, we may assume that the conditions of our experiments actually resemble the conditions encountered clinically<sup>20</sup> as closely as experiments with animals with normal hearts will permit.

The functional tests used in this connection were essentially five, e. g., phenolsulphonaphthalein, lactose, salt, potassium iodid and water. In our earlier studies the excretion of certain other dye substances was studied in certain cases as was also the glycosuria following the injection of phloridzin. It became apparent early that nothing was to be gained from the continued use of indigo carmin and carbol fuchsin (rosanilin) in this connection,<sup>21</sup> inasmuch as they were excreted roughly in propor-

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20 We are aware that in certain respects differences do exist. Although in the pressure exerted a similar relative disproportion exists in the two conditions, naturally where the *vis a tergo* is normal the absolute pressure may be greater. Furthermore, there is a possibility that the insufficient oxygenation of blood generally, in broken compensation, plays a rôle in determining renal function. We do not think so much in this connection about the diminished oxygen supply to the kidney as of the possible toxicity of the waste products of other organs which suffer from lack of oxygen, affecting renal function.

21 Personal observations to be published later. For discussion of these tests, see also publication of Rowntree and Geraghty, *Jour. Pharm. and Exper. Therap.*, 1910, 1, 579.

tions paralleling the excretion of phthalein. The use of the indigo carmin was discarded, since its colorimetric properties are not well adapted to accurate quantitative work. Both drugs are excreted much more slowly than is the phthalein. The glycosuria following the administration of phloridzin seems to bear some relation to the excretion of lactose under similar conditions, e. g., glycosuria is prolonged. Phloridzin glycosuria, however, is exceedingly variable under any conditions and it was considered more advantageous to use only lactose, on which greater reliance can be placed.

In some of our later experiments observations were made on the urea and nitrogen content of the blood, which has been considered by Prevost and Dumas<sup>22</sup> (1821), Christison<sup>23</sup> (1834), Bright<sup>24</sup> (1836), Frerichs<sup>25</sup> (1851), Ascoli<sup>26</sup> (1901), Strauss<sup>27</sup> (1902), Muller<sup>28</sup> (1904), Obermeyer and Popper<sup>29</sup> (1911), Hohlweg<sup>30</sup> (1911), Widal<sup>31</sup> (1911), von Noorden<sup>32</sup> (1907), to be materially augmented wherever marked decrease in the excretory capacity of the kidney exists.

A brief description of these various tests, together with the technic, follows.

*The Phthalein Test* was used according to the original technic described by Rowntree and Geraghty.<sup>33</sup> One cubic centimeter of a phenolsulphonephthalein solution containing accurately 6 mg. was injected under antiseptic precautions into the lumbar muscles of the dogs, which were then placed in metabolism cages. A catheter was passed at the expiration of an hour and ten minutes and the total urine for this period collected. The urine was made distinctly alkaline, diluted to 1 liter, and the amount of drug present determined by the use of our<sup>34</sup> modification of the Autenrieth-Königsberger colorimeter. In our previous work with this test we have already determined that the output for normal dogs is 50 per cent., or more, for this period.

22 Prevost and Dumas 1821. Cited by Schondorff, Pflüger's Arch f d ges Physiol, 1899, lxxiv, 307.

23 Christison. On Granular Degeneration of the Kidney, 1834.

24 Bright. Guy's Hosp Rep, 1836, 1, 358.

25 Frerichs. Die Bright'sche, etc., 1851.

26 Ascoli. Pflüger's Arch f d ges Physiol, 1901, lxxxvii, 103.

27 Strauss. Die chronischen Nierentzündungen in ihrer Einwirkung auf die Blutflussigkeit und deren Behandlung, 1902.

28 Moller. Verhandl d Deutsch path Gesellsch, 1904-5, vii-ix, completing No 80.

29 Obermeyer and Popper. Ztschr f klin Med, 1911, lxxii, 332.

30 Hohlweg. Deutsch Arch f klin Med, 1911, civ, 216.

31 Widal. Bull et mém Soc méd d hôp, Paris, 1911, Series 3, xxxii, 627.

32 Von Noorden. Metabolism and Practical Medicine, 1907, ii, 486.

33 Rowntree and Geraghty. Jour of Pharm and Exper Therap, 1910, 1, 579.

34 Rowntree and Geraghty. THE ARCHIVES INT MED, 1912, ix, 284.

The lactose, potassium iodid, salt and water tests, which have received a thorough study at the hands of Schlayer<sup>35</sup> and his coworkers in relation to the renal function in experimental acute toxic and vascular nephritides, and also in relation to nephritis as it exists clinically, were applied to this study of the renal function in chronic passive congestion. Schlayer's technic was adhered to as closely as possible.

Lactose was shown by Voit<sup>36</sup> to be excreted quantitatively by the kidneys following subcutaneous or intravenous administration. De Bonis<sup>37</sup> showed that lactose was excreted by the glomeruli. Schlayer therefore adopted it as a means of determining the functional capacity of the glomeruli in various forms of experimental nephritis and in the nephritides encountered clinically. He admits that its excretion is delayed in passive congestion, and therefore in his clinical studies he avoided cases which exhibited cardiac inefficiency. He considered delay in lactose excretion to be evidence of functional derangement of the vascular system. Since it is a substance foreign to the body and consequently not subjected to the many extrarenal factors which influence the excretion of water, he places his chief reliance on this test for information concerning the vascular functional capacity. Schlayer worked with rabbits and administered the lactose intravenously. We have worked with dogs, injecting it into the lumbar muscles.

Since De Bonis does not claim that lactose is not excreted by way of the tubules but merely that it is well excreted by the glomeruli, we thought that the frog's kidneys might furnish valuable information in regard to the mechanism of the excretion of lactose. Nussbaum<sup>38</sup> showed that the tubules in the frog's kidney are supplied by the renal-portal system which is entirely separate and independent of the arterial supply of the glomeruli. This work has been confirmed by Beddard,<sup>39</sup> Cullis,<sup>40</sup> and Rowntree and Geraghty.<sup>38</sup> An attempt was, therefore, made to see if the frog's kidney could excrete lactose in the absence of the glomerular system.

Large male frogs, *Rana catesbeiana*, weighing about 300 gm, were pithed, their abdomens opened by long incisions on each side of and parallel to the anterior abdominal vein. The left kidney was exposed and all the arterial connections severed by means of the Paquelin cautery.

35 Schlayer and Takayasu. *Deutsch Arch f klin Med*, 1910, xcvi, 17, 1911, ci, 333, and Schlayer, 1911, cii, 311.

36 Voit. *Deutsch Arch f klin Med*, 1897, lvi, 545.

37 DeBonis. *Giorn Internat d sc med*, 1907, xix, 446, 451.

38 Nussbaum. *Pflüger's Arch f d ges Physiol*, 1878, xvi, 179, xvii, 580.

39 Beddard. *Jour Physiol*, 1902, xviii, 20, see also Bambridge and Beddard. *Jour Physiol*, 1906, xxiv, Proc of Physiol Soc p ix, and *Biochem Jour*, 1906, i, 255.

40 Cullis. *Jour Physiol*, 1906, xxxiv, 250.

as suggested by Beddard. A cannula was then inserted into the anterior abdominal vein and a small glass cannula inserted into the left ureter. Protocols will indicate the course of the experiment and the results obtained.

#### PROTOCOLS OF EXPERIMENT

I Ringer's solution was perfused from a Mariotte flask through the renal-portal system under a pressure of 35 cm of water. Perfusion for fifteen seconds every three minutes was begun at 12 30 and continued until 12 50, no urine being secreted. At this time sufficient sulphonephthalein to make a 1 per cent solution was added to the Ringer's solution and perfusion continued until 1 30 p m, still no urine being excreted. Sufficient urea and lactose were then added to make a 1 per cent solution of the former and an 8 per cent solution of the latter and the perfusion continued. At 1 45 the urinary flow started, phthalein making its appearance but lactose being absent. At 2 p m sugar was recovered from the urine excreted.

II Ringer's solution was perfused from a Mariotte flask through the renal portal system under a pressure of 35 cm of water. Perfusion for fifteen seconds every three minutes was continued from 3 30 p m to 4 p m without any flow of urine. At 4 p m, sufficient lactose to make a 0.5 per cent solution was added to the perfusing fluid. Urinary flow started at 4 15 p m. A trace of sugar was in the urine at 4 45 p m. Phthalein (6 mg) and sufficient urea to make a 2 per cent solution were added to the perfused fluid at 5 p m. At 5 30 p m the urine contained sugar and phthalein.

The kidney was perfused at 5 p m with a saturated solution of Prussian blue, immediately removed and placed in absolute alcohol. Serial sections were made but no blue found in the glomeruli.

From this it is seen that the frog's urinary tubules are capable of excreting lactose. We feel, therefore, that sufficient proof has not been presented that lactose is excreted by the glomerular system entirely.

From a repetition of Schlager's work on acute toxic nephritis and our own, as well as his experience with its use as a functional test clinically, and from the evidence presented in this study, we feel that the mechanism of its excretion differs essentially from that of phthalein, salt, indigo carmin, etc. Throughout this investigation we have used it as Schlager did as an index of the condition of the vascular function of the kidney, admitting, however, that we need much more information concerning the manner and significance of its excretion.

#### TECHNIC

Our technic was as follows. 3 gm of lactose in 15 c c of distilled water was injected into the lumbar muscles under aseptic precautions. The animals were placed in metabolism cages, catheterized at the end of four hours, and thereafter every half hour up to eight and nine hours. The total amount of lactose excreted in four hours was determined polarimetrically in a great many instances by the Schmidt and Haenisch instrument, but since the time necessary for total elimination is considered by Schlager to be of greater importance, we have studied this more particularly. The presence of lactose in the urine has been determined by means of the Fehling and Nylander tests. The total time necessary for complete excretion of lactose under such conditions normally does not exceed six hours.



*Potassium Iodid Test*—Potassium iodid was one of the first substances to be utilized in connection with functional renal studies, being introduced by Duckworth<sup>41</sup> in 1867. It appears quickly in the urine following its administration by mouth, Quetsch<sup>42</sup> stating that it appears in nine to eighteen minutes after a 2 gm dose, Roux<sup>43</sup> thirteen minutes after a 3 gm dose, and Studeni<sup>44</sup> thirteen to eighteen minutes after a 1 gm dose. The time required for complete elimination, as stated by different authors, varies markedly. According to Geisler,<sup>45</sup> 6 gm require twenty-five hours, Roux, 5 gm require thirty hours, Studeni, 1 gm requires thirty to thirty-six hours. Anten,<sup>46</sup> 0.5 gm requires forty hours, Schlager and Takayasu<sup>47</sup> and Monokow,<sup>48</sup> 0.5 gm requires forty-eight hours. Schlager, in his studies, however, did not consider anything less than sixty hours to be a delayed excretion time following 0.5 gm by mouth.

According to the studies of Schlager, potassium iodid is excreted by the tubules of the kidney and on it he has placed most dependence in determining tubular functional capacity. Anten<sup>46</sup> showed that the excretion is not hastened by the occurrence of diuresis. It has been claimed by Schlager and Takayasu<sup>47</sup> that its excretion is not influenced by chronic passive congestion and that it is not delayed in cases of cardiac decomposition, characteristics which, if true, would make it of tremendous importance in differentiating cases of pure passive congestion of the kidney from passive congestion associated with nephritis.

In our studies 0.5 gm of potassium iodid was administered by stomach tube and its presence in the urine determined by Sandow's<sup>49</sup> test. This amount we have found normally to be excreted within forty-eight hours, but, like Schlager, we have considered a delayed excretion only that which continues for more than sixty hours.

In certain instances, on account of vomiting, the drug was given directly into the blood by means of an intracardiac injection. Following such administration it is entirely eliminated normally within twenty-four hours.

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41 Duckworth. St Barth Hosp Rep, III, 216.

42 Quetsch. Berl klin Wehnschr, 1884, XXI, 353.

43 Roux. Thèse de Paris, 1890, No 248. Experiences sur l'élimination des jodures par l'urine.

44 Studeni. Untersuchungen über die physiologische Ausscheidung der Jod-preparate durch den menschlichen Harn. Zurich, 1897.

45 Geisler. Cited by Anten (Note 46).

46 Anten. Arch f Path u Pharm, 1902, LVIII, 331.

47 Schlager and Takayasu. Deutsch Arch f klin Med, 1911, CI, 354.

48 Monokow. Deutsch Arch f klin Med 1911, CI, 309.

49 Sandow's method consists of adding 1 c c of 2 per cent sodium nitrite solution and 1 c c of 10 per cent  $H_2SO_4$  to from 10 c c to 30 c c of urine, followed by the addition of a small amount of chloroform. This is shaken together and allowed to separate into layers, the presence of the iodid being indicated by a purplish-red or violet color in the chloroform.

*The Salt and Water Tests* —The excretion of salt following its administration in amounts greatly in excess of that ordinarily taken with the food, is accomplished by the tubules, according to Schlayer. Normally a large amount of salt is excreted by one of two methods. If it is given without extra water it is almost entirely excreted within twenty-four hours, without diuresis, by increased salt concentration in the urine, if given with an excess of water it is excreted partially through increased concentration in the urine and partially through diuresis.

Where vascular injury to the kidney exists we may have the simple administration of salt followed by a marked diuresis, all of the salt being smoothly excreted in twenty-four hours without its percentage content in the urine being at all increased. This is usually associated with a somewhat low and fixed specific gravity and the syndrome is spoken of as "vascular hyposthenuria." Here the inability to concentrate is not due to any incapacity of the tubules to excrete salt, but on hypersensitive vessels which respond to the salt administration with a diuresis. In more severe vascular injury the vessels do not act in the same way, oliguria characterizing the urinary picture. In severe tubular destruction, a urine of fixed low specific gravity is obtained, the quantity of which is not materially affected by the administration of salt and the salt content of which is not augmented by administration of extra amounts of salt because of the inability of the tubules to excrete it. Such a condition is known as "tubular hyposthenuria."

In this study the daily excretion of salt, both as to per cent and total excretion, was first observed, the animal being kept on a constant diet. An extra 3 gm of salt were given by mouth and the effect on the percentage content in the urine and on the total salt output for the following twenty-four hours determined. In certain instances, where administration of the salt by mouth produced vomiting, 1.5 to 2 gm of salt were given intravenously or directly into the heart by an intracardiac injection. The Lutke-Martius<sup>50</sup> method was used throughout in the chlorid determinations.

#### VARIOUS METHODS OF PRODUCTION OF CHRONIC PASSIVE CONGESTION OF KIDNEYS

In order to obtain passive congestion of the kidneys, bands were placed, by the technic described above, on one or both renal veins, on the vena cava above the entrance of the renal veins, on the aorta below the origin of the renal arteries, while simultaneously vessels concerned in the establishing of collateral circulation were ligatured, the production of hyperemia was attempted by placing a band about the aorta below the

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50 Sahli Diagnostic Methods, 1911, 177

level of the renal arteries. The urinary picture, functional renal capacity and pathological findings obtained following these various methods are indicated below

#### A BAND ON THE VENA CAVA ABOVE ENTRANCE OF RENAL VEINS

The effect of placing a constricting band on the vena cava just above the entrance of the renal veins, without handling the kidneys or interfering in any way with their collateral circulation, is shown in the following protocols:

##### HOUND BITCH I—Weight 15 kg

February 3 Was etherized A band was placed about the inferior vena cava just above the entrance of the renal veins, constricting the cava to about one-third its normal size

February 4 Animal is apparently feeling very well, eats and drinks normally and is playful

February 5 and 6 Urine<sup>51</sup> shows a trace of albumin a few hyaline and granular casts, no red blood-cells or pus Phthalein output normal—70 per cent in an hour Lactose excretion delayed, 50 per cent excreted in four hours, positive after eight hours

February 14 and 15 Wound has healed perfectly Dog apparently in normal condition

Urine Albumin a trace, negative for blood, pus or casts Phthalein normal, 52 per cent in an hour Lactose excretion slightly delayed, 27 per cent for four hours, still faintly positive at seven hours Salt well concentrated

February 27 and 28 Animal appears normal Phthalein 65 per cent Potassium iodid, forty-eight hours Lactose, six hours 3.7 gm salt excreted on a 3 gm intake Salt concentrated good 1.2 per cent The kidneys are therefore functionally normal

April 22 to 24 Animal is normal apparently Urine shows a trace of albumin, but sediment contains no abnormal elements Phthalein 60 per cent Potassium iodid 48 hours Lactose slightly delayed—seven hours

May 13 Animal is pregnant Urine excreted in fair amounts Specific gravity 1.040, slight trace of albumin No casts or blood Phthalein and salt normally excreted while potassium iodid requires sixty hours Lactose more delayed than at last observation, still strong in urine after eight hours

June 1 The bitch gave birth to a litter of pups Her condition was excellent No functional studies were made

##### BITCH II—Weight 7.2 kg

January 31 Band placed about inferior vena cava just above entrance of renal veins Ether anesthesia lasting one hour

February 1 and 2 Animal in excellent condition, behaves normally Urine contains albumin  $\frac{1}{4}$  to  $\frac{1}{2}$  per cent, shows a few granular casts and epithelial cells Phthalein output is normal, 60 per cent Phloridzin glycosuria persisted four hours Lactose excretion delayed urine strongly positive for sugar at end of eight hours

February 5 Excreted 150 cc of urine on a 500 cc fluid intake Intake of salt 5.4 gm with only a trace excreted Urine shows only a slight trace of albumin and a few hyaline and granular casts

February 19 to 23 Animal apparently normal Phthalein 60 per cent for one hour Lactose is delayed, urine reacting strongly at end of seven hours Salt excreted in good concentration, 2 per cent—4 gm output on 5 gm intake Potassium iodid requires seventy to 100 hours for excretion

March 8 Dog has developed distemper Chloroformed

51 All urinalyses here recorded were made on catheter samples

From these experiments it is evident that a moderate obstruction to the inferior vena cava above the level of the renal veins causes no serious change in the renal function. A persisting mild albuminuria is produced which is associated early with the presence of casts. The urinary output is fair in amount. The excretion of lactose is markedly delayed, salt excretion may be somewhat slow at first, but later is normal. The potassium iodid was delayed in one animal, normal in the other. The phthalein was absolutely normal throughout. That no serious injury to the renal function is produced is evidenced by the subsequent history of the animal. Eventually a practically normal functional picture is obtained, although slight albuminuria persists.

#### BANDS ON BOTH RENAL VEINS

BITCH III—Weight 35 kg

December 19 Moderately tight bands placed on both renal veins

December 21 and 22 Urine small in amount, shows albumin and numerous red cells but no casts. The phthalein was excreted in a mere trace on the 21st, and 8 per cent for one hour on the 22d. Only a trace of rosanilin excreted.

December 26 Animal is feeling badly, walks about but does not eat. Vomits after drinking small quantities of water. Wound is infected. Phthalein and rosanilin were injected but no trace of them could be found in urine at end of one hour. Urine is very scanty, containing albumin and blood.

December 28 Found dead. No careful study of the condition of the renal veins as to thrombosis or slipping of the band, etc., was made.

BITCH IV—Weight 10 kg

January 22 Bands placed about both renal veins causing marked congestion.

January 23 Animal is exceedingly playful. Phthalein output 52 per cent.

January 25 to 31 Animal in excellent condition. Urine is normal in amount and contains albumin  $\frac{1}{8}$  to  $\frac{1}{4}$  per cent. On some examinations the sediment contains a few hyaline and granular casts and a few red blood cells while at other examinations sediment is normal. The phthalein is excreted normally, 52 per cent in one hour. Rosanilin is also well excreted. Potassium iodid is markedly delayed, 100 hours being required for total excretion. Lactose is markedly delayed, while salt is excreted normally—1.4 per cent and absolute output 5 gm on a 5.2 gm intake. The glycosuria following phloridzin is very slightly prolonged.

February 14 and 15 Animal in excellent condition. Phthalein output 65 per cent. Salt excreted well 1.5 per cent concentration and 6.5 gm absolute on a 6 gm intake. Potassium iodid excretion still delayed—eighty hours. Lactose slightly delayed—six to seven hours. Urine plentifully excreted, 500 cc on 600 cc intake of water. Sediment negative for pus, blood and casts.

February 20 The abdomen was again opened. Both kidneys were seen to be enlarged and markedly engorged. The capsular veins were strikingly enlarged and tortuous. The left kidney was removed for histological study. The band was found in place surrounded by fibrous tissue and the veins not thrombosed.

#### A BAND ON LEFT RENAL VEIN, RIGHT-SIDED NEPHRECTOMY

A more pronounced grade of congestion was attempted through a right-sided nephrectomy and a band about the vein of the remaining kidney. The effect of such a procedure on the renal function was studied on several dogs, the results appearing in Table 1.

TABLE I -

RENAL FUNCTION OF A RIGHT SIDED NEPHROCTOMY WITH BAND ON LEFT VULVA

Dog	Wt, Kg	Date 1912	Condition	H <sub>2</sub> O, cc	Urine				Lactose, Hrs	KI, Hrs	Salt			Remarks															
					Quantity, cc	Sediment	Albumin	Phthalain			Ins	Out gms	Per Cent																
V	7.9	1/12	Good	200	120	Many R B C Hyaline and granular casts	++	26	8°+	24 Intra-cardiac	Trace	25	21	Operation, rt kidney removed, wt 30 gm Moderately tight band on left renal vein Phloridzin glycosuria 7° on 13th Indigocarmin 5 per cent in 1 hr on 14th Carbol-fuchsin 11 per cent in 3 hrs on 15th Animal chloroformed Left kidney showed marked chronic passive congestion Wt 50 gm No venous thrombosis Peritonitis															
		13		300	270			03				18																	
		14	Depressed	Depressed	350	16	+	72				11	23		22	Trace	5	Chloroformed Kidney was found to have an accessory renal vein No marked congestion was found											
		16	100																200	100	100	100	100	100	100	100	100	100	100
		17	Very sick																100	100	100	100	100	100	100	100	100	100	100
VI	5.4	1/12	Good	300	180	Occasional R B C	+	25	8°+	72	Trace	11	23	Operation, rt kidney removed Moderately tight band on left renal vein Phloridzin glycosuria 7° on Jan 13 Carbol-fuchsin 45 per cent in 3 hrs on 15 Phloridzin glycosuria 6° on Jan 15 Indigocarmin 7 per cent in 2 hrs Jan 17 Phloridzin glycosuria 5° on the 29 Carbol-fuchsin 40 per cent in 3 hrs on Jan 29															
		13	Good	250	210			90 (25°)				30	15		22	Chloroformed Kidney was found to have an accessory renal vein No marked congestion was found													
		14	Good	300	277	Occas R B C 1/8 to 1/4%+ hyaline and gran casts	1/8 to 1/4%	52				72	18		5		13												
		15	Excellent	400	180													Hyal and cell casts, R B C	65	8°	8°	34	13						
		17	Excellent	400	180																			Hyal and cell casts, R B C	65	8°	8°	34	13
		1/23-26	Excellent	400	180	Hyal and cell casts, R B C	65	8°				8°	34		13														
		1/29-31	Excellent	400	180												Hyal and cell casts, R B C	65	8°	8°	34	13							
		2/9	Excellent	400	180	Hyal and cell casts, R B C	65	8°				8°	34		13														
		2/13	Distemper	400	180												Hyal and cell casts, R B C	65	8°	8°	34	13							
						Hyal and cell casts, R B C	65	8°				8°	34		13														
				Hyal and cell casts, R B C	65				8°	8°	34			13															

IV	10 0	2/20 2/21 3/18 5/13 5/24	Good Thn  Excellent Excellent	  300 300 300	421 300 300	Few hyal and gran casts, epith cells  Blood and pus cells, few red cells	++ + +	40 55 56	8°+  8	66  60	4 2  2 6 3 0	1 6 2 4 2 4	39 8 8	One month previously dog had had bands placed on both renal veins, 2/20/12 left kid- ney removed May 24 animal very lively and playful The right renal vein was tied and animal lived on the collateral venous return *
VII	9 6	1/29 2/1 5 6 3/21-22 3/30 4/1	  Good Good Thn	  700 800 500	70 440 550 300	Few hyal and cell casts, few R B C  Numerous R B C and W B C, no casts, normal	1/4 to 1/2% + 0 Trace	54 50 75 67	8°+  8°+  8°+	  48	5 4 5 0 3 0	1 6 1 2 2 2	38 20 1 1	Two anesthetics as vagina was slit open 3 days previously Left kidney wt 34.5 gm Tight band on right renal vein Phloridzin glycosuria 4° on Feb 1
VIII	6 0	1/27 29 31 2/18-23 4/22 5/8	Excellent Good Good Good	 300 300 500	 400 100 370	  Normal	1/8 to 1/4% 0 +	 80 55 70	8°+ 7°+ 6°+ 7°	100     	5 2     	3 0     	73     87	Left kidney removed, tight band on left renal vein Car- bol-fuchsin 35 per cent after 3° on 29 Phloridzin glyco- suria 5° on 30 May 15, renal vein tied Animal lived on collateral venous return *

## EFFECT ON RENAL FUNCTION OF LIGATING COLLATERAL AS WELL AS RENAL VEINS

Dog	Wt, Kg	Date 1912	Condition	Sp Gr	H <sub>2</sub> O, cc	Urine						Salt			Remarks	
						Quan- tity, cc	Sediment	Albu- min	Phtha- lein	Lac- tose	KI, Hrs	In, Gms	Out, gms	Per Cent		
IX	60	3/5														Right kidney removed Wt 28.5 gm Moder- ately tight band on left renal vein, ovarian and lumbar veins ligated  General infection 12th — found dead Thrombosis of renal vein Large subcapsu- lar hemorrhage Kid- ney weight 50 gm
		6 & 7	Good	1018	700	500	No casts	++	54.0	8°+	48	3.0	3.0	6		
		9 & 10	Distemper	1012	500	450			12.0			3.0	63	14		
		11					Many red blood cells, no casts		Trace	8°+		.				
X	65	3/18														Right kidney weighing 24 gm removed Moder- ately tight band about left renal vein, ova- rian, lumbar and su- prarenal veins tied Animal killed—throm- bosis of renal vein at site of band Kidney wt 40 gm No periton- itis Kidney markedly congested
		19	Good	1032			Numerous hyaline and granular casts, no blood	+	47.0	7°+	72					
		21	Fair	1018	500	400			9.0			3.2	2.4	61		
		22							7.5							
		23		1018	500	300	Blood, pus and epith, no casts	++	11.5							
		24							11.5							
		25	Fair						15.0							
		26		1016	500	670			12.0	8°+	60	4.0	1.4	16		
		28	Very sick	1018				+	11.0							
		29					Blood, pus and casts	+	5.0							

XI	60	3/20 21  23 24 28	Good  Excellent Dead	1047 1039			Few epithelial cells W B C	++  	320 500 600								Right kidney removed Wt 24 gm Moderately tight band on left renal vein Ovarian, lumbar and suprarenal tied 28th — found dead Band in place No thrombosis Cause of death unknown Heart and lungs negative No peritonitis
XV	80	4/19 20 22 26 27 28	Fair Distempered Dead	1024	400		Casts, hyaline and granular Occasional cast	++  0	600 360 480	7°+ 6°	48	20	Tiace				Right kidney removed Left kidney banded fairly tight Ovarian tied at entrance to renal Typical bronchopneumonia, beginning thrombosis of left renal vein Kidney showed marked congestion and some cloudy swelling
XII	85	3/26 27  28	Chloroformed  Very sick  Chloro-		few cc Anuria	few cc	Much blood, hyal., granular casts	++  	00								Right kidney removed Wt 34 gm Left renal vein tied Chloroformed Kidney 52.5 gm Showed marked congestion
XIII	95	4/4 5			few cc		Full of blood	+  	00								Right kidney removed, weighing 45 gm Very tight band on left renal vein All collaterals tied Right renal vein thrombosed Wt 60 gm
XIV	45	4/11 12 13 14		1006	200	325	Blood and casts	+  	15 15	8+	Intra-cardiac 24	Intra-cardiac 20	75	23			Right kidney removed Wt 13.8 gm Left kidney banded, access collaterals cut Left kidney 28 gm at autopsy Veins thrombosed Marked congestion



From a study of this table it is at once evident that a kidney subjected to such usage does not suffer seriously over any great period of time. Even on the day following the operation the animal may appear normal. The urine is fair in amount, contains some albumin, red blood-cells, a few hyaline and granular casts, but the phthalein output in many instances is little, if any, reduced. The lactose, however, is invariably delayed markedly, the excretion of potassium iodid is usually considerably delayed and the salt not well excreted. As time progresses it becomes more apparent that the functional injury is slight—the phthalein output rapidly increasing to normal, if it has been at all reduced. Weeks or months after the operation the animal is normal to all appearances. A urinalysis, however, usually reveals a trace of albumin, in which microscopically a few granular and hyaline casts are seen. A functional study shows normal phthalein, iodid and salt excretion, while the lactose is slightly delayed.

The establishment of a good collateral circulation was thought to be probably responsible for the rapid return to normal of the kidney function.

The effect of ligating the vessels chiefly involved in collateral circulation of the kidney simultaneously with the operation described above was investigated. The band was placed about the renal vein at its entrance to the inferior vena cava. The ovarian vein, at its entrance to the renal, as well as one of its branches, a large vein which passes from the lower pole of the kidney to the ovary, was ligated. In some instances one of the lumbar veins and the suprarenal vein were also tied.

The results obtained from a study of this series of animals are shown in Table 2. These animals can be divided into two groups. Group I, including animals IX, X, XI and XV, in which the bands were of moderate tightness only, and Group II, in which the bands were made very tight. All four animals of Group I show a normal, or only slightly reduced, phthalein output at first. The quantity of urine excreted was large, contained albumin, but blood and casts were absent in two animals. The lactose was markedly delayed in all, salt excreted fairly well in two, and the iodid normally in two and delayed in another.

Dogs IX and X both showed a sudden marked drop in the phthalein output four or five days after the operation. The first subsequent examination of the urine showed large numbers of red blood-cells, probably indicating the occurrence of thrombosis in the renal vein, inasmuch as thrombosis was encountered at autopsy in each case. Dog X was particularly interesting, living for more than a week with a low phthalein output, the lactose, salt and iodid excretion being also very low. The urine was plentiful and of low specific gravity, contained much albumin, numerous red cells and a few casts. The dog throughout this period was

only in fair condition, at times playful and sprightly, but on the whole inclined to lie quietly and to sleep. Vomiting occurred at intervals.

Dog XV differed from the others of this group in that only one collateral channel was ligated, e g, the ovarian vein just at its entrance to the renal vein. On the third day following operation the animal was only in fair condition. The urine was large in amount, containing considerable albumin and casts. The phthalein and iodid output were normal, while lactose was markedly delayed and salt excreted with great difficulty. At this time it became apparent that the dog was developing distemper. Later, on the seventh to the ninth days the albumin had disappeared and the only abnormal constituent present in the sediment was an occasional cast, the phthalein output being practically normal — 42 per cent. On the ninth day the animal died, the autopsy revealing a marked typical bronchopneumonia, no peritonitis, an immense left kidney with a tremendous amount of collateral circulation and beginning thrombosis, localized in the vein at the site of the band.

Group II is composed of two dogs, XIII and XIV. The bands placed on the renal veins of these dogs were very small. In Dog XIV the ovarian, and the veins at the lower pole which empty into the ovarian, lumbar and suprarenal veins were ligated. Both animals were exceedingly sick from the time of operation until death. Dog XIII excreted only a few cubic centimeters of urine after the operation. This was full of blood and no phthalein was recovered within an hour. The animal died after forty-eight hours. The kidney was found much enlarged, the band in place, with thrombosis of the vein. A tremendous subcapsular hemorrhage, the blood having partially dissected the capsule, was found. The kidney showed marked chronic passive congestion.

Dog XIV excreted 325 c c of urine on an intake of 200 c c of water on the day following operation. The urine contained albumin, blood and casts. The phthalein output was only 1.5 per cent, and the lactose markedly delayed. As the animal was vomiting repeatedly, the salt and iodid were administered by an intracardiac injection. The iodid was entirely excreted within twenty-four hours, but the salt was poorly excreted. Again on the following day only a trace of phthalein was recovered. The animal died on the fourth day. The kidney was double the normal size with the band in place. The vein was patent at the site of the band, but thrombosed distally. The capsular and ovarian veins were markedly engorged and a peculiar fleshy-like tissue (probably hemorrhage) was found between the layers of the capsule in the region of the pelvis of the kidney. The animal also showed some bronchopneumonia.

To show the similarity of Cases XIII and XIV, from the point of view of urinary and pathological findings, to the picture following a

sudden complete ligation of the renal vein after removal of the opposite kidney, the data relating to Dog XII is included in this table. On the day following operation the animal was very ill and only a few cubic centimeters of bloody urine could be obtained on catheterization. This contained casts of various kinds—hyaline, granular and blood. After this no urine was obtained. At autopsy the kidney was found to weigh 52.5 gm (R 34 gm) and to be dark violet in color. Between the layers of the capsule and in the tissues just outside of the capsule about the renal and ovarian veins was a large hemorrhage with clots of dark blood of varying age. The glomeruli were very distinct and markedly congested—more so than in any other kidneys met with in this study.

COLLATERAL CIRCULATION OF THE KIDNEY FOLLOWING GRADUAL BUT  
COMPLETE OCCLUSION OF THE RENAL VEIN AND THE  
CONDITION OF RENAL FUNCTION UNDER  
THESE CIRCUMSTANCES

It has been suggested in the earlier part of this paper that great importance is to be attached to the development of collateral circulation following gradual and progressive occlusion of the renal vein. An effort has been made to ascertain just how important collateral circulation may become in determining the state of renal function under such conditions.

Following the application of the band to the renal vein in dogs the capsular, ovarian, lumbar, suprarenal and ureteral veins become markedly engorged and distended. These enlarged vessels present a striking vascular picture which has been previously described by Litten.

The extent and tremendous importance of this development of collateral circulation is indicated by the following protocols.

Dog VIII—Weight 6 kg, had the right kidney removed and a moderately tight band placed about the left renal vein on January 27. Three months later the renal function had returned to normal save for a slight albuminuria and a slight delay in lactose excretion. A second operation was performed May 16, at which time it was seen that a tremendous collateral circulation involving the capsular, ovarian, lumbar, and suprarenal veins, had been established and that the renal vein itself was relatively small. The renal vein was tied and the abdomen closed. The animal's venous circulation, therefore, was entirely collateral. On the day following the operation urine was secreted which contained a large amount of albumin, blood and casts, but the phthalein excretion was 50 per cent for an hour. During the next two days the animal was in good condition. The lactose was delayed over eight hours, but salt and iodid were excreted normally. At the present time, two weeks later, albuminuria and delayed lactose excretion still persist, otherwise the animal seems perfectly normal.

Dog IV—Weight 10 kg, had bands placed about both renal veins on Jan 22, 1912. In the course of a few weeks function had returned practically to normal. On February 20 a second operation was performed, the left kidney being removed. The animal made a perfect recovery and the functions quickly again returned to practically normal. On May 24 a third operation was performed. The right kidney was found to be greatly enlarged and associated with a tremendous collateral circulation. The renal vein was tied at its entrance to the vena cava, the

abdomen closed and the animal allowed to recover. On the following day the dog was in good condition with a fair urinary secretion (250 c c) containing albumin, blood and casts. The phthalein output was 40 per cent. Two days later the lactose was found to be delayed for more than eight hours. Salt and iodid were excreted normally. The animal was in excellent condition, but the wound was badly infected.

In two instances this remarkable condition has been seen, e g, an animal living in apparently good health, secreting practically a normal urine and exhibiting an excellent condition of renal function with the renal vein tightly ligated. This affords striking evidence of the great importance of collateral circulation where gradual obstruction to the venous return from the kidney develops.

Although, owing to different anatomical conditions in humans, so great a development of collateral circulation may not be possible, it undoubtedly is a matter of extreme importance where gradual venous obstruction occurs.

To summarize, then, it is evident that, after a one-sided nephrectomy, the application of a moderately tight band about the other renal vein causes marked congestion of the remaining kidney. The congestion is associated at first with the production of a good quantity of urine which contains usually albumin and casts and sometimes blood. The excretory capacity of the kidney is not seriously injured, as evidenced by a good phthalein output. The excretion of lactose is always markedly delayed, as is usually also that of the iodid and salt. With the development of a good collateral circulation the congestion becomes less intense, the albumin, blood and casts become a less pronounced feature of the urinary picture. The phthalein, iodid and salt may all be normally excreted, but the lactose is still delayed. Two or three months after such an operation the most probable abnormalities will be a very slight trace of albumin and a delayed lactose excretion.

When a moderately tight band is applied and the collateral channels ligated, the same picture is encountered during the following two or three days as is seen when the collaterals are left open. Thrombosis of the renal vein is apt to develop, however, and its occurrence is associated with the appearance of a large amount of blood in the urine and a sudden marked fall in the phthalein excretion. Nausea and vomiting develop. The amount of urine at first may be large. All the excretory functions finally fail and death ensues.

When an excessively tight band is applied to the renal vein and the collateral channels are ligated, the effect is usually similar to that which would be encountered following complete ligature, e g, large amounts of albumin and blood, together with the excretion of minimal traces of phthalein, lactose, iodid and salt. Thrombosis occurs and death results.

The magnitude and importance of the development of collateral circulation following gradual obstruction to the return venous flow is indicated by the demonstration of the possibility of animals living and exhibiting a good renal function where the occlusion of the renal vein has been gradual, but complete

THE EFFECT OF PLACING A BAND ABOUT ONE RENAL VEIN, THE OTHER  
KIDNEY REMAINING UNDISTURBED URETERAL CATHETERIZATION OF BITCHES

Experiments were also made for the purpose of determining the effect on the urinary picture and on the total renal function of applying a band to one renal vein, the other kidney being undisturbed. Simultaneously, a comparative study was made of the urine from a normal kidney and that from a kidney with chronic, passive congestion in the same animal. By such a method it is possible to determine the effect *per se* of congestion on function.

In order to determine the function of each individual kidney it was, of course, necessary to collect the urine separately from the two sides. This was done by means of ureteral catheterization and was accomplished without discomfort to the dog. The animal was tied down on its back with comfortable holding straps and the ureteral catheters introduced in the manner constantly employed in the clinic.

In order to use the ordinary instruments for ureteral catheterization, large bitches are necessary. It would be possible to use comparatively small bitches if a single-barrelled catheterizing instrument large enough to carry a single No. 6 F catheter were employed. In order, however, to catheterize both ureters, and at the same time carry catheters large enough to obturate them effectively, an instrument of at least 24 F must be employed. The ureteral orifices are readily recognized in the bitch, and as a rule but little difficulty is encountered in entering them. But, owing to the curved course of the ureter in the vesical portion, passing the catheter higher than 2 cm frequently requires considerable manipulation.

The Brown-Buerger catheterizing cystoscope No. 24 F and No. 6 flute-end catheters were used in all of our experiments. When the internal orifices cannot be recognized readily, an injection of indigo carmin intramuscularly will, within a few minutes, clearly indicate their positions.

BITCH XVI<sup>1</sup>—Weight 18 kg, showed a normal renal function as determined by functional tests. On January 18, a moderately tight band was applied about the left renal vein. Five days later the phthalein output was practically normal.

On February 9, both ureters were catheterized without anesthesia by the technique described above. The urine was obtained for twenty minute periods as follows:

TABLE 3—URINE FROM BITCH XVI WITH BAND ON LEFT RENAL VEIN

## FIRST PERIOD

Amount, cc		Sulphone- phthalein, Per Cent		Indigo Carmin, Per Cent		Sp Gr		Urea, Gm	
Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
19	*10	63.3	100	59.0	100	1.010	1.030	0.0145	0.015

## SECOND PERIOD

21	13	64.7	100	64.1	100	1.005	1.014	0.015	0.021
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\*The urine from the side having the smaller amount was diluted to the quantity of the other and then the two urines compared in the Duboseq colorimeter. The diluted urine of the right side was much more intensely colored than that of the left. In these tables the relative amount of dye substance of the side containing the smaller amount is expressed as percentage of the other.

TABLE 4—URINARY FINDINGS IN BITCH XVI AFTER 300 c.c. WATER BY STOMACH TUBE

## FIRST PERIOD

Urine cc		Sp Gr		Sulphone- phthalein, Per Cent		Indigo Carmin, Per Cent		Sodium Chlorid, Per Cent	
Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
67	50	1.010	1.017	79.0	100	78	100		

## SECOND PERIOD

60	70	1.010	1.019	73.2	100	67	100	0.20	0.36
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## THIRD PERIOD

43	69	1.010	1.010						
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February 16, 300 c.c. of water was given by stomach tube one half hour before catheters were in place. The right ureter was catheterized and the urine of the left side collected transvesically. The leakage was practically zero—not more than 0.5 c.c. for any period of twenty minutes.

On March 19, a phthalein test was made in the usual way, showing an output of 70 per cent in one hour

On April 3, the animal was killed by bleeding, owing to severe septic infection from a wound in the leg. The kidneys were found to be of about equal weight, 48 gm each. The band was in place, exerting but moderate pressure on the vein, which was patent and free from thrombosis. The cut surface of the kidney did not exhibit marked evidence of congestion. There was thinning of the cortex in two or three areas at the lower pole, over which areas the capsule was found to be adherent. The capsular veins of the left kidney were markedly engorged and there was considerable enlargement of the vessels concerned in the collateral circulation.

**BITCH XXII**—Weight 8 kg, was subjected to operation on May 10 and a moderately tight band placed about the left renal vein. Ten days later the animal was in excellent condition, the phthalein output normal. Chlorbutanol was administered by stomach tube, the lower abdominal wall opened in the median line and the bladder exposed. The urethra was tied and the bladder sewed down the middle from the urethra to the apex of the bladder, with a fine needle and fine silk. A glass bladder cannula was then placed in each half of the bladder. In order to start urinary secretion it was found necessary to inject 40 cc of 5 per cent NaCl solution intravenously. The urine was then collected from each side separately for one hour periods. The results of these studies are tabulated below.

TABLE 5—URINARY FINDINGS IN BITCH XXII WITH BAND AROUND LEFT RENAL VEIN

FIRST PERIOD

Urine, cc		Sp Gr		Sulphone- phthalein, Per Cent		Urea, Mg Per cc		Indigo Carmin, Per Cent		Lactose, Gm		Carbol- fuchsin, Per Cent	
Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
167	140	1.013	1.009	83	100	4	10						

Total phthalein output 46 per cent for one hour

SECOND PERIOD

164	150	1.034	1.035			10	15			1.1	1.1		
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THIRD PERIOD

105	124	1.031	1.028					93	100				
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FOURTH PERIOD

108	112	1.015	1.007									60	100
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Total N from 10 cc of mixed urine from left side, 0.0536 gm

Total N from 10 cc of mixed urine from right side, 0.0658 gm

On opening the abdomen the left kidney appeared considerably larger than the right and a good collateral circulation had developed. In order to demonstrate that there was no communication between the two halves of the bladder, water was slowly injected into one half, and recovered through the corresponding catheter, without any flow from the other side. The animal was killed by bleeding. The right kidney weighed 25 gm and the left 25.5 gm.

These experiments are interesting and instructive from several points of view. A greater excretion of urine has been encountered on the side where the venous return was obstructed in several observations which, in one case, extended over a period of weeks. *This bears out the contention of Schwarz as to the possibility of encountering increased urinary output with obstruction to venous return, and directly disproves the claims of Paneth and de Souza.* It shows, further, that even in the presence of the relative polyuria on the congested side that the per cent of solids, as indicated by the phthalein, indigo-carmin, lactose, urea and salt content, is greater from the normal than from the congested side. The experiments further suggest that the water goes by preference through the slightly congested kidney, whereas the excretion of solids is considerably interfered with. The uniform relative excretion of the same dye on different occasions, as well as the parallelism of the excretion of different dyes at the same observation, is exceedingly striking. The truth of Albarran's claim, *i. e.*, that with forced fluid the extra demand for secretion is responded to by the normal kidney, is demonstrated by the greater output of water from the right kidney in the second and third period of the first experiment. The excess from the right kidney began at the proper period at which the polyuria should appear. The fact that the water only, and not the salt, lactose, carbol-fuchsin, the indigo-carmin and phthalein, are increased is also significant.

#### BANDS ON THE AORTA BELOW LEVEL OF RENAL ARTERIES

A greater quantity of blood was directed through the kidney by cutting off to a considerable degree its escape from the aorta below. Moderately tight bands, which constricted the aorta to approximately half its normal diameter, were applied just above its bifurcation. This experiment alone was performed on one animal, combined with a nephrectomy on a second, and with nephrectomy and a band on the renal vein on the third. The following protocols indicate the results.

BROCK XVI—Weight 5.5 kg, operated on February 12. A fairly tight band was placed on the aorta below the renal arteries so that the vessel was decidedly larger above and smaller but still pulsated below the band.

February 13-16. Dog in excellent condition. Normal quantity of urine containing a few hyaline and granular casts. Phthalein and salt excreted normally, iodid delayed to seventy hours. Lactose delayed to seven hours.

February 27-28. Phthalein, salt, iodid and lactose all excreted normally. Animal in good condition. Here we have an entirely normal renal function.



March 4 Animal developed distemper and died

Autopsy Bronchopneumonia No peritonitis The aortic band is in place buried in fibrous tissue The aorta is patent, standing out well above band, but is much smaller below The kidneys are probably slightly enlarged, and combined weight 50 gm, are dark blue in color

Hyperemia, therefore, caused the appearance of casts in the urine, together with a delayed lactose and iodid output, which rapidly returned to normal

Bitch IX—Weight 7 kg, had a right-sided nephrectomy and a tight band about the aorta just above its bifurcation, on February 17 On the following three days the animal was in poor condition, showing evidences of peritonitis The urine output was rather small in amount, the phthalein and iodid normal, lactose delayed and salt poorly excreted On the 23rd the animal was chloroformed The autopsy revealed peritonitis and retroperitoneal abscesses The band was found in place, the aorta enlarged above it The kidney was dark, purplish-red in color, deeply engorged and weighed 45 gm The capsule strips readily

Dog XVIII—Weight 9 kg, March 4 had a right sided nephrectomy performed, the kidney weighing 38.5 gm A band was placed on the aorta just above its bifurcation, causing marked constriction, and a second band of moderate size was placed about the renal vein at its entrance into the vena cava

March 5 Animal in good condition exhibiting a polyuria—1,000 cc output on 700 cc water intake Urine contains a trace of albumin and a few hyaline casts, but no blood cells The phthalein output is reduced to 20 per cent Lactose delayed to seven hours, iodid normal The salt is excreted poorly in low concentration, 09 per cent, yielding a total of 9 gm on a 3 gm intake

March 6 Polyuria persists—900 cc urine on 700 cc water intake Salt concentration low—0.11 per cent

March 7 Phthalein output normal, 50 per cent Polyuria 750 cc on 700 cc intake Salt concentration is low—0.12 per cent

March 8 Phthalein normal, lactose delayed—eight hours, iodid seventy two hours The fluid excretion was not noted

March 11 Phthalein normal, 60 per cent Animal shows signs of distemper developing Urine contains a trace of albumin, but no casts or blood

March 13 Animal died with symptoms of distemper At autopsy the kidney was found intensely congested Weight 60 gm Both bands were in place and both vessels patent An abscess containing about 5 cc of pus was found in the region of the aortic band Some fibrinous peritonitis was also found

This experiment is of peculiar interest on account of the occurrence of a definite persisting polyuria associated with venous obstruction, which coexists with an excessive amount of blood flowing into the kidney

#### CONTROLS

It was considered desirable to see what effect on the renal function was produced by simple unilateral nephrectomy The first dog, in addition to a right-sided nephrectomy, had the left renal vein isolated from the surrounding tissue just as is done in each of the experiments when the band is applied

Dog XX—Weight 6.9 kg, nephrectomy performed on February 26

February 27 Phthalein 57 per cent Iodid eighty hours Lactose eight hours + Sodium chlorid excreted in good concentration

March 18 and 19 Urine normal in quantity No albumin or blood, an occasional hyaline cast The phthalein output was normal, as was also the salt The lactose was very slightly delayed—6½ hours, but the iodid was not excreted in less than seventy-two hours

April 14 The phthalein, salt, iodid and lactose were absolutely normally excreted, and the urine itself was entirely normal

Dog XXI—Weight 5 kg, April 24 Right kidney removed, weight 17.8 gm

April 25 Phthalein 38 per cent, slightest trace of albumin, an occasional cast seen in centrifugalized specimen

April 27 Phthalein normal—55 per cent Lactose delayed seven hours, salt excretion somewhat delayed

May 3 to 9 The salt, lactose and phthalein excretions are all normal, the only abnormal urinary feature being a very faint trace of albumin

Simple one-sided nephrectomy in a healthy dog, therefore, causes but slight change in the renal function which is of short duration

#### INCOAGULABLE NITROGEN OF THE BLOOD IN CHRONIC PASSIVE CONGESTION

In five cases of animals with a moderate degree of chronic passive congestion, and with relatively normal renal function, and in one with marked congestion, the incoagulable nitrogen of the blood was estimated. The technic employed was as follows: 10 c c of blood was withdrawn from the heart and placed in 115 c c of 95 per cent alcohol to precipitate the albumin. This was filtered, and 100 c c of the filtrate evaporated to dryness. The total nitrogen of this residue, representing 8 c c of blood, was estimated by Kjeldahl's method. In the five nearly normal cases, the nitrogen was not increased above 0.50 gm per liter of blood. In the dog with advanced congestion, the nitrogen was increased to 0.60 gm per liter.

It can be concluded, therefore, that mild experimental chronic passive congestion in dogs does not produce an accumulation of incoagulable nitrogen in the blood.

#### HISTOLOGICAL STUDY

The histological study<sup>52</sup> of the kidneys removed at autopsy was made as follows. The kidneys were fixed in formaldehyd solution or Zenker's fluid, cut and stained with hematoxylin and eosin. The microscopic study in all cases revealed varying degrees of chronic passive congestion of all the vessels and capillaries. In certain of the cases there were foci of leukocytes or small abscesses. In one case there was considerable increase in connective tissue suggesting a chronic nephritis. Whether this was due or not to the congestion cannot be stated. On the whole, histologically, it seems that by this method, chronic passive congestion of varying intensity is produced without an accompanying chronic nephritis.

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<sup>52</sup> A further study of the histological changes following more prolonged chronic passive congestion is intended.

## CONCLUSIONS

1 By the technic described it is possible to produce over short periods any grade of chronic passive congestion desired

2 Slight experimental chronic passive congestion of the kidney is characterized by (a) a normal quantity of urine which contains a trace of albumin, intermittently a few hyaline and granular casts and occasionally a few red blood-cells, (b) the functional capacity varies but little from normal, since phthalein, salt and potassium iodid may be all normally excreted, while lactose excretion is but slightly delayed

3 Moderate experimental passive congestion of the kidneys is characterized by (a) a fair amount of urine containing albumin, casts and frequently red blood-cells, (b) a total excretory capacity which is apparently not markedly decreased, since the phthalein excretion is usually normal. The excretion of salt is usually somewhat decreased, that of potassium iodid variable, that of lactose invariably delayed

4 Marked experimental chronic passive congestion of the kidneys is characterized by (a) very scanty amounts of urine containing a large amount of albumin, casts and red blood-cells, (b) a much reduced functional capacity, since the phthalein, salt and lactose excretions are markedly delayed, as is also frequently that of iodid

5 Albuminuria is almost a constant accompaniment of experimental passive congestion, casts are usually present, and red blood-cells appear if the congestion is of any considerable degree

6 Lactose excretion is the first to become affected by increasing grades of chronic passive congestion, then the excretion of salt and iodid, and lastly, that of phthalein

7 The phthalein test gives the most reliable information concerning the degree of renal insufficiency in experimental chronic passive congestion. Marked delay in the excretion of lactose, iodid and salt has, indeed, been encountered in animals showing a normal phthalein output. These animals were, however, apparently in good general condition, while subsequent events showed that they remained in good condition. On the other hand, a marked decrease in phthalein excretion has invariably been associated with the development of clinical manifestations, indicating renal inadequacy and followed by death. The phthalein test is, therefore, the test of greatest prognostic importance in chronic passive congestion

8 Lactose, while of least value in revealing the degree of involvement of renal function in experimental chronic passive congestion of the kidney, is of the greatest value in detecting its existence. It is, therefore, of these tests that of greatest diagnostic, but of least prognostic value

9. The excretion of potassium iodid is usually prolonged in experimental chronic passive congestion of the kidney. The time of elimination of this drug is, however, so variable that the test proves practically valueless in this connection.

10. The excretion of sodium chlorid is usually decreased where moderate or marked experimental passive congestion is present.

11. Partial obstruction to venous return through the renal vein is not invariably associated with decreased urinary secretion. In an apparently normal unanesthetized or anesthetized (chlorbutanol) animal which has partial occlusion of one renal vein only, more urine is sometimes excreted from the congested kidney, while the solids are excreted in greater concentration from the normal side.

12. Where gradual progressive obstruction to the renal vein occurs, the development of a collateral circulation is of great importance in maintaining the functional capacity of the kidney since an efficient renal function may be encountered when the venous return from the kidney is entirely collateral. On the other hand, ligation of collateral vessels, simultaneously with a moderate degree of obstruction to the renal vein, usually results in renal inefficiency and death.

13. An excessive flow of blood through the kidney simultaneously with an obstruction to its outflow may be followed by polyuria.

14. Mild grades of experimental chronic passive congestion are not associated with the accumulation of incoagulable nitrogen in the blood.

15. Varying degrees of chronic passive congestion which are unassociated with nephritis are produced by the above-described procedures.

# AN EXPERIMENTAL STUDY OF POISON OAK\*

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While it is true that poison oak and its sister plants have rarely, if ever, caused a death, it is also true that a large majority of people living in the temperate zones find their enjoyment of the country seriously curtailed by the menace of these noxious plants. And besides this restriction of healthful pleasures, there is an unestimated monetary loss to laboreis and construction companies operating in infested regions, which I am sure is not inconsiderable. Yet in spite of these well-known facts, very little has been attempted, and still less accomplished, to abate this wide-spread evil.

## SKETCH OF PLANT

The plants specially referred to are poison oak (*Rhus diversiloba*), poison ivy (*R. toxicodendron*) and poison sumach (*R. venenata*), which form a widely distributed group. The poison ivy<sup>1</sup> is found in abundance throughout the United States as far west as eastern Texas, eastern Kansas and Minnesota, and in greater or less abundance throughout the less arid regions of the west, with the exception of California and the western parts of Oregon and Washington, where it appears to be entirely replaced by the poison oak. The plants are very similar to each other, each being a shrub that trails along the ground, or climbs fences, trees or brush, or in many instances stands erect independently. It does not frequent the higher mountains. The irregularly lobulated and dentated leaves of the poison oak are a beautiful red when young, and an equally attractive russet when old, rendering them enticing to the uninitiated. The fine hairs that are found on the leaves, especially along the margins, are supposed by some to carry the poison when wafted by breezes, thus explaining poisoning at a distance. The berries and blossoms are green and extremely poisonous. But the berries turn white as they ripen, lose their poison and are often eaten by birds, which are the means of distributing the plants over so wide a territory.

## THE TOXIC PRINCIPLE NON-VOLATILE

While poison oak, poison ivy and poison sumach differ botanically, their juices seem to be chemically identical. Franz Pfaff,<sup>2</sup> of the Harvard

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\*From the Hearst Laboratory of Pathology and Bacteriology, University of California

\* Manuscript submitted for publication in THE ARCHIVES Nov 25, 1912

1 Chestnut Farmer's Bulletin No 86, U S Dept Agr culture

2 Pfaff Jour Experimental Medicine, 1897, (2), 181

Medical School, in his excellent monograph, states that the poison is identical in the ivy and in the oak. That the dermatitis caused by either plant is identical clinically, has been recognized for a long time. Several attempts have been made to isolate chemically the poisonous principle of the plants. This problem is of special importance because it underlies much of the clinical and biologic work.

The earliest attack on this difficult problem was made in 1779 by van Mons,<sup>3</sup> who concluded that the poison was a "gaseous hydrocarbon," emanating from the plant only at night or on cloudy days. Lavin, writing thirty-three years later (1825), also believed the poison to be a gas exhaled at night, but thought it was not a hydrocarbon. Another thirty-three years then elapsed before Kirtell (1858) analyzed the plant and derived his "rhustannic acid." But he said that there was also a volatile, toxic alkaloid. In 1865, Maisch isolated his "toxicodendric acid," again a volatile substance. Then followed two Japanese, Ishimatsu and Yoshida (1882 and 1883), who also concurred that the toxic agent is volatile. The chemical problem really had but little light thrown on it until Pfaff approached the problem from the clinical viewpoint and showed that Maisch's "toxicodendric acid" is entirely inert, indeed, nothing but acetic acid, and that contrary to all previous impressions, the toxin is actually a non-volatile substance which he extracted and named "toxicodendrol" on account of its oily appearance. Of this substance, as little as 1/1,000 mg suffices to produce the typical dermatitis.<sup>2</sup> All parts of the plant yield toxicodendrol, the leaves and green berries, however, more in proportion to weight. The best and most recent chemical study of the toxin is that of W. A. Syme,<sup>4</sup> whose dissertation on "Some Constituents of the Poison Ivy," was accepted by Johns Hopkins University in granting him the degree of Ph.D. in 1906. His analysis shows that the poison is a complex substance of a glucosidal nature, yielding, on analysis, gallic acid, fisetin and rhamnose. The poison was again shown to be non-volatile, even when mixed with acetic acid (with which it is naturally associated in the plant), or with alcohol.

Thus it is seen that for a hundred and eighteen years, from van Mons to Pfaff, the opinion prevailed that the toxin was volatile—a natural conclusion in the presence of the common observation that persons are poisoned while simply passing near the plant, without actual contact. The importance of Pfaff's work, confirmed and enlarged by Syme, is therefore evident. Before dismissing the subject of the nature of the poison, it may be noted that a bacterial theory had its supporters, but its proponent (Burrill, 1882) admitted (1895) that proof was lacking. That

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<sup>3</sup> L. E. Warren has compiled an extensive and excellent bibliography in *The Midland Druggist and Pharmaceutical Review*, 1910, xlv, Nos. 3, 4 and 5.

<sup>4</sup> W. A. Syme, *Johns Hopkins Univ. Bulletin*, 1906, "Some Constituents of the Poison Ivy Plant."

the poison is not bacterial is to-day very clear, although bacteria often play an important rôle as agents in secondary infection

#### POISONING WITHOUT CONTACT

The toxic principle having been shown to be non-volatile, the practical question immediately presents itself, how does poisoning at a distance occur? That persons are poisoned without direct contact with the plant is too common an observation to be denied. The explanation is doubtless the mechanical transportation of the poison, as happens when the pollen, or the plant hairs, or other dust from the plant is carried by air-currents. Or, perhaps as commonly, the transporting agents are simply clothes, or tools or animals, which, after brushing against the plant, are able to transfer the poison to susceptible persons. Such explanations are easily acceptable when one remembers how minute a quantity suffices to induce inflammation. In order to show that the poison is not volatile the following experiment was made

*Experiment 1*—Young, fresh poison oak leaves were crowded into a glass tube, one end of which was closed with cotton. Holding this end against the skin of a susceptible person, air was blown through the tube. The spot struck by the air current was then covered with zinc oxide plaster to retain what poison might have been deposited, and after forty eight hours the spot was inspected. Were the poison volatile, dermatitis should have resulted. The result was negative.

On the other hand, I was severely poisoned by the dust raised while handling the dried plants in the laboratory

#### SMOKE FROM BURNING PLANTS IS POISONOUS

Another fact of interest, amply sustained by popular personal testimony, is that the smoke of burning rhus plants is especially toxic. This is somewhat surprising after reading Pfaff's statement<sup>2</sup> that "toxicodendrol is decomposed easily by heat." The degree of heat required is not mentioned. On this point the following experiment was made

*Experiment 2*—Fresh green leaves were placed in a test tube closed with cotton, and submerged (except the open end) in boiling water for one hour. Dermatitis was readily secured by contact with the boiled leaves, thus showing that the poison is not destroyed by 100 C. for one hour.

The literature presents no evidence on this point. The above experiment supports the popular belief that smoke from burning rhus (especially if the plant is green) carries the poisonous juice of the plant. It is probable that in a heated state the juice more readily penetrates the epidermis and causes toxic inflammation.

*Experiment 3*—In order to make this test more positive, dried rhus leaves were crowded into a glass tube, to one end of which was attached a rubber mouth piece. The glass was then held in the flame until the leaves burned. While blowing gently through the tube, the smoky current was caused to impinge on the skin

of a susceptible person. The spot was then covered with zinc oxid plaster to retain what poison may have been deposited. Characteristic dermatitis developed in twenty-four hours.

#### THE OCCURRENCE OF THE ERUPTION

Because the spots of dermatitis often break out successively in widely separated areas of the skin, the impression has gained credence that the poison is distributed by the blood-stream—a matter of considerable importance in its bearing on the pathology and treatment of the disorder. Light was thrown on this question by Pearson (1880), who showed experimentally that serum from the vesicles is not toxic. I have repeatedly tried in vain to produce dermatitis by rubbing in the serum from vesicles. Chestnut<sup>1</sup> also concludes that the dermatitis is purely local, and is never distributed by the blood. The following experiment is deemed conclusive on this point:

*Experiment 4*—I frequently poisoned limited skin areas and prevented any spread of the toxin by covering it immediately with zinc oxid plaster. Under these conditions a dermatitis never occurs in any other than the exact spot where the toxin is applied.

It is easily conceived, however, that in natural exposures several elements would tend towards the occurrence of dermatitis in crops rather than at all points simultaneously. Before all the poison has penetrated, some of it might easily be transferred to other areas, thus producing a new crop. Again, the poison might be transferred to new areas from clothes or hair. Furthermore, it is not unlikely that where the skin is thin, as on the face, wrists, etc., the time necessary for penetration—the latent period—is shorter than where the skin is thicker—again accounting for succession rather than for simultaneity.

#### PHYSIOLOGICAL PATHOLOGY

The exact physiological nature of the poisoning by rhus juice has never been studied. This is not surprising when one realizes that the exact nature of the toxin is still not fully known. The chemical problems must first be solved before the physiologist can offer any explanation of why this peculiar glucoside should cause inflammation. That there are variations in general or local susceptibility in different individuals and in the same individual at different times, cannot be doubted. But the exact property of cells or fluids of the body that determines susceptibility to rhus is as yet a mystery.

#### RELATION TO SWEAT REACTION

Misled by Maisch's statement that the poison was an acid, I made a series of observations some years ago on sweat reactions as determined by litmus paper, to see whether acidity or alkalinity of the sweat bears any relation to susceptibility to the poison.



*Experiment 5.*—A number of sweat reactions were taken and recorded, each person being asked whether he was susceptible to the poison. Of each class—acid, alkaline, and neutral—there were some susceptible and some immune. Among them was one person with strongly acid sweat who was extremely susceptible. But there was another equally susceptible whose reaction was strongly alkaline. So that no relation to sweat reaction could be determined even though account was taken of the physiological change of reaction during exercise.

#### VACCINATION AND IMMUNITY

Considerable popular testimony is available upholding the possibility of vaccination against rhus by ingestion of the plant or its derivatives. There are those who state that the tincture of the fluid extract taken internally prevents attacks on subsequent contact with the plant. Likewise, many persons claim to have gained immunity by chewing or eating small quantities of the rhus leaves. This prophylactic measure is said to have been found valuable by the engineers of the Union Pacific Railroad Company while the line was being built through poison oak country. Similar testimony is obtained from residents in the Adirondack Mountains. And I am told by an eye witness that Indians and other residents of New Mexico habitually eat the leaves each spring to avoid poisoning during the summer. Experimental confirmation or scientific observation of these folk-sayings is, however, entirely lacking. But they open the large question of acquired immunity. Ford<sup>5</sup> states that there is no difficulty in showing that many persons are quite resistant to the action of rhus toxin. On the other hand, the same writer expresses the opinion that the so-called natural immunity is really an acquired immunity. He raises the question, obviously difficult to answer, whether "the cases of supposed natural immunity do not occur in individuals in whom as children the effects from handling the plant have gradually worn off, the original dermatitis having been so insignificant as to have escaped notice, or being so many years distant as to have been forgotten." He concludes that complete natural immunity, when put to experimental test, is exceedingly rare. Warren<sup>6</sup> likewise thinks that "the belief in absolute immunity is a delusion." Desiring to settle this question by experimental evidence I made the following tests.

#### EXPERIMENTS ON IMMUNES

*Experiment 6.*—A B claims he acquired immunity through several severe attacks. A fresh rhus leaf was applied to each forearm and held in place by plaster. Both applications caused marked dermatitis.

*Experiment 7.*—E L claims natural immunity from birth. A fresh rhus leaf was applied to each arm and held in place by plaster. Slight dermatitis was caused on each arm.

5 W W Ford "Antibodies to Glucosides with Special Reference to Rhus Toxicodendron," *Journal Infectious Diseases*, 1907, iv, No 4

6 L E Warren "The Poisonous Principle of Rhus," *Pharmaceutical Jour*, Oct 30, Nov 6, 1909

*Experiment 8*—D S claims acquired immunity except from the smoke A fresh leaf was applied to each arm and held in place by plaster Both spots showed dermatitis

*Experiment 9*—J C claims natural immunity from birth She therefore offered to gather rhus leaves for me While bringing them in she held them as one does a bouquet, against her chest The waist being cut low permitted the leaves to touch the skin Numerous mild spots of dermatitis developed

*Experiment 10*—E F claims immunity from birth She accompanied J C gathering leaves But she developed no dermatitis Believing her immune, she was engaged to gather a larger quantity of leaves After this exposure of about three hours among the February leaves, she developed numerous troublesome spots

*Experiment 11*—L A claims immunity from birth Tested with tincture of rhus on forearms, he developed red itching spots

*Experiment 12*—A R claims immunity from birth He never has been poisoned, though exposed

Test 1 Rubbed fresh green leaves on forearm Result negative, though observed for one week

Test 2 Put active tincture on arm Result negative after several days

Test 3 Applied alcohol solution of pure toxin to the wrist Result negative after three days

Test 4 Applied same to forearm and covered with plaster Result negative after three days

Test 5 Applied active tincture rhus to forearm, covered with zinc oxid plaster Result negative after several days

Test 6 Believing him immune, he was sent to gather a sack of leaves Eleven days later he noticed spots of dermatitis with itching and his face became swollen Rhus dermatitis was markedly developed on face and arms

Thus of seven "immunes" tested, all responded to the poison *This indicates universal susceptibility to this toxin*

#### ANIMAL IMMUNITY

Whether immunity can be induced experimentally in animals is an important problem that was attacked by W W Ford<sup>5</sup> (1907) His experiments were done on rabbits and guinea-pigs, using fresh fluid extract of *Rhus toxicodendron* He states that after subcutaneous injection of a toxic dose, there elapses a latent period of seven or eight days in which the animal loses weight and dies at the end of another week of nephritis Incidentally, a slough is formed at the site of injection The estimated toxic dose for a 250 gm guinea-pig was 0.25 c c, and for an 800 gm rabbit, 1 c c On the basis of these toxic doses, he gave repeated small doses at intervals of a few days, and claims to have immunized animals so that they resisted successfully five or six times their fatal dose

Such immunized animals showed no nephritis when killed The serum from these immunized animals protected other animals completely against fatal doses of fluid extract of rhus Thus Ford appears to have produced active and passive immunity in these animals These results, however, are inconclusive because of the unfortunately small number of experiments, and because of the material used—the fluid alcoholic extract, which contains, besides an indefinite amount of rhus toxin, various unde-

terminated extractives of the plant, some glycerin, and as much as 58 per cent of alcohol. Furthermore, in a personal communication Ford states that he was unable to get the same results a second time, attributing the failure to impotency of the fluid extract.

#### COMMERCIAL FLUID EXTRACT OF RHUS

An attempt was made to repeat Ford's work on animals, but the doses he found to be toxic were without effect. The material used was Wyeth's fluid extract of *Rhus radicans*.<sup>7</sup> The result is seen in Table 1.

TABLE 1—SUBCUTANEOUS INJECTIONS OF GUINEA-PIGS WITH WYETH'S FLUID EXTRACT OF RHUS RADICANS, CONTAINING 58 PER CENT ALCOHOL

No. Pig	Weight, Gms	Wyeth's Fl'd Ext c c	Time Observed, Days	Result
1	585	5	5	In 24 hours sick, dead 5 days
5	240	3	1/6	Drunk 5 minutes, dead 1 day
9	440	1	16	Negative, gained weight steadily, no induration

Although the larger doses kill guinea-pigs, controls with the corresponding amount of alcohol alone, died, and exhibited the same induration and necrosis at the injection site as described by Ford (see Guinea-pigs 10, 18, 20 and 19, Table 2).

TABLE 2—GUINEA-PIGS RECEIVING SUBCUTANEOUS INJECTIONS OF ALCOHOL

No. Pig	Weight, Gms	Alcohol, c c	Per Cent	Water, c c	Time Observed, Days	Result
8	280	1 0	95		19	Induration and necrosis
6	210	3 0	95			Drunk, dead in few minutes.
4	335	3 0	95			Drunk, dead in few minutes
10	440	1 5	95		17	Stupid, large necrosis, died
18	410	1 0	60		2	Site softened, wt=420 gm
18	420	2 0	60		10	Large necrosis, wt=250 gm, died, no nephritis
20	310	2 0	60	2 0	9	Drunk, necrosis, wt=250 gm, died, infected, no nephritis
19	360	2 0	98	1 0	11	Drunk, necrosis, wt=220 gm, died, infected, no nephritis

Tables 3 and 4 seem to indicate that the alcohol solution of rhus toxin is somewhat more toxic than the same amount of alcohol alone. However, the short time intervening between the injection and death argues in favor of the alcohol alone being responsible for the death. This is referred to later.

<sup>7</sup> *Rhus toxicodendron*

TABLE 3—RESULTS OF INTRAVENOUS INJECTIONS OF 95 PER CENT ALCOHOL IN RABBITS

Rabbit No	Weight, Gms	Alcohol, 95 Per Cent	Time Observed Days	Result
10	2140	0 5	4	Negative
6	1050	1 0	7	Negative
10	2040	1 0	2	Negative
4	2560	1 0	1	Negative
5	1500	1 0	1	Negative
7	780	2 0	1½	Died

TABLE 4—RESULTS OF INTRAVENOUS INJECTIONS OF ALCOHOLIC SOLUTION OF RHUS TOXIN IN RABBITS

Rabbit No	Weight, Gms	Toxin, Gms	Alcohol, 98 Per Cent, c c	Time Observed Days	Result
6	1015	0 0125	0 5	5	Negative
6	1160	0 0125	0 5	7*	Negative
10	2240	0 0125	0 5	7	Negative
4	2550	0 0125	0 5	7	Negative
4	2560	0 01625	0 65		Died immediately
9	2045	0 025	1 0		Died immediately
11	2580	0 025	0 5	46	Negative
8	1900	0 05	2 0		Died immediately

\*Additional

Not desiring to work further with a substance containing an unknown quantity of the poison, besides alcohol, glycerin and other undetermined substances in considerable quantities, the plant was collected and the pure toxin extracted after the method recommended by Syme. Fresh leaves of poison oak are thoroughly extracted with absolute alcohol. After filtration, lead acetate in water is added till precipitation is complete. The precipitate is then washed well and dried at a low temperature, when it is extracted in Soxhlet extractors for at least ten hours. The ether extract is then mixed up with water and treated with hydrogen sulphid, to separate the lead. The water and ether are then separated, the ether filtered, and well washed, after which it is evaporated at a low temperature. The presence of the toxin is then confirmed by testing for glucoside (Molisch's test) and by application to the skin, the physiological test. This toxin was carefully weighed and dissolved in absolute alcohol, so that 1 c c contained 0 0125 of pure toxin.

## INTRAVENOUS ADMINISTRATION OF SUSPENSION

Noting that alcoholic menstrua, such as the fluid extract, produce marked induration at the site of subcutaneous injection, thus rendering problematic the amount of toxin entering the general system, it was determined to introduce the toxin intravenously. But both alcohol and ether when employed in workable quantities, intravenously, cause clotting of the blood, obliterating the vessels, and resulting in rapid death from heart

clots After studying various other possible solvents for the toxic glucosid,<sup>8</sup> a suspension was finally settled on It was prepared by taking the desired dose of toxin dissolved in absolute alcohol, and mixing it with freshly sterilized distilled water (0.5 to 2 c.c.) This yields a suspension of the toxin so fine that it does not separate after standing for several months The addition of normal saline solution, however, does cause it to precipitate inside of forty-eight hours That this suspension is still toxic was proved by tests on my arm Such a suspension is readily and safely introduced into the blood-stream without causing clotting or death in the doses used

TABLE 5—INTRAVENOUS INJECTIONS OF RABBITS WITH SUSPENSION OF RHUS TOXIN

Rabbit No	Weight, Gms	Toxin, Gms	Alcohol, c c	Water c c	Time Observed, Days	Result
10	2360	0.03125	125	375	5	Negative
10	2280	0.03125	125	375	6*	Negative
10	2180	0.125	5	5	5*	Negative
10	2260	0.125	5	5	8*	Negative
12	1650	0.25	1	2	30	Negative
16	2410	0.228	1	2	30	Gained weight
16	2675	0.228	1	1	11*	Dead, pleuro-pneumonia, no nephritis
15	2300	0.456	2	2	23	Negative
13	2170	0.684	3	2	30	Site necrosed
18	1700	0.456	2	1		Died immediately

\*Days additional

The suspension was also given to guinea-pigs, subcutaneously, as shown in Table 6, without deaths from the toxin, though it caused induration and necrosis at the site of injection

TABLE 6—SUBCUTANEOUS INJECTION OF GUINEA-PIGS WITH SUSPENSION OF RHUS TOXIN

Pig No	Weight, Gms	Toxin, Gms	Alcohol, c c	Water, c c	Days Observed	Result
12	470	0.125	5	75	21	Slight induration
13	330	0.125	5	75	21	Slight induration
14	500	0.25	10	15	17	Induration and necrosis
15	280	0.3875	15	35	12	Induration and necrosis
16	300	0.228	10	1	33	No nephritis Necrosis Died
17	430	0.456	2	1	29	No nephritis Necrosis Died

8 The toxin is insoluble in glycerin or in rabbit serum

## COMPARISON OF DOSAGE

In my extraction of the rhus plants, I found that the plant yields in pure toxin about 1/1,000 of its weight. One c c of the fluid extract used represents 1 gm of the plant. From these data it is assumed that 1 c c. fluid extract contains 0.001 pure toxin. But the fluid extract is made by extracting the plant with 65 per cent alcohol, whereas I used 95 per cent., which extracts much more toxin. The disparity of toxicity was also clearly demonstrated by tests on my arm. So that while the above dosage appears small, the toxicity as compared with the fluid extract is satisfactory. Thus while Ford found 0.25 c c fluid extract fatal for a 250 gm guinea-pig, the dose in terms of pure toxin, 0.0031 gm, or 0.000123 gm toxin per gram weight of pig, is very much smaller than I was able to give—0.03875 gm or 0.001385 gm toxin per gram weight of pig, as illustrated by Guinea-Pig 15, Table 6. And even in terms of fluid extract, if one might assume that the extract Ford used was of equal toxicity to mine, I was able to give a larger dose, as illustrated by Guinea-Pig 9, Table 1. The doses I used were not fatal, the deaths occurring from intercurrent diseases, and showing no nephritis.

## CUTANEOUS TESTS

From clinical observation of human cases, and from the internal administration to animals,<sup>2</sup> the toxin appears to have a selective action for epithelial cells. For this reason it is customary to experiment on the cutaneous surfaces of animals. Observations of this character indicate clearly that individuals of the same species vary widely in their susceptibility to rhus poisoning, as witnessed by the following experiments on rabbits and a monkey (Table 7). Of ten rabbits tested by applying rhus poison to shaved spots on the outer surface of their ears, seven failed to develop any dermatitis at all. Although the pure toxin was applied thoroughly to the thin skin of the monkey, the test was absolutely negative, observed for one month.

TABLE 7—RESULTS OF APPLYING RHUS TOXIN TO THE SKIN OF ANIMALS

Rabbit No	Materials Used	Time Observed	
		Days	Result
1	Fluid extract	90	Negative
3	Pure toxin	18	Negative
5	Pure toxin	14	Negative
4	10 per cent tinct	14	Negative
2	Green leaves	2	Positive
6	Pure toxin	14	Positive
4	Pure toxin	5	Positive
11	Alcohol sol toxin	14	Negative
18	Alcohol sol toxin	14	Negative
17	Alcoholic sol toxin	14	Negative
Monkey	Pure toxin (left eyelid and chin)	30	Negative

## THE ANTIGENIC PROPERTIES OF RHUS TOXIN

The possibility of producing an antitoxic serum is so attractive that special study was made as to the possibility of artificial immunization of animals. My experiments on this point indicate clearly that the toxin is not in itself fatal for rabbits and guinea-pigs, and, therefore, no antitoxic action of an immune serum could be tested on these animals. It is, however, well known, that the Bordet-Gengou fixation reaction serves to detect antibodies in an immune serum and the demonstration of such substances was sought for in rabbits that had received several doses of the toxin. The test was made with the sera of three animals, treated as follows

TABLE 8—RABBIT 19 IMMUNIZATION INTRAVENOUS INJECTIONS OF SUSPENSION OF RHUS TOXIN

Date	Weight, Gms	Toxin, Gms	98 Per Cent Alcohol, c c	Water c c	Results
Aug 6	1920	0.0228	1	1	Normal
Aug 9	1980				Edema of ear
Aug 10	2040	0.0228	1	1	
Aug 14	2020				
Aug 16	1970	0.0228	1	1	
Aug 20	2030	0.0228	1	1	Large necrosis of ear
Aug 27					Bled to death for serum

TABLE 9—RABBIT 15 IMMUNIZATION INTRAVENOUS INJECTION OF SUSPENSION OF RHUS TOXIN

Date	Weight, Gms	Toxin, Gms	98 Per Cent Alcohol, c c	Water c c	Results
Aug 10	2190	0.0228	1	1	Normal
Aug 14	2260	0.0228	1	1	
Aug 16	2230	0.0228	1	1	
Aug 20	2180	0.0228	1	1	Large necrosis ear
Aug 25					Littered six
Aug 27					Bled to death for serum

TABLE 10—RABBIT 13 INTENSIVE IMMUNIZATION INTRAVENOUS INJECTION OF SUSPENSION OF RHUS TOXIN

Date	Weight, Gms	Toxin, Gms	98 Per Cent Alcohol, c c	Water c c	Results
Aug 10	2190	0.0456	2	2	Normal
Aug 14	2160	0.0228	1	1	Normal
Aug 15	2150	0.0228	1	1	Edema of ears
Aug 16	2140	0.0228	1	1	
Aug 20	2160				Large necrosis ear
Aug 24	2180				Bled to death for serum

With the sera from these supposedly immunized animals, viz Rabbits 19, 15 and 13, the fixation test was done as indicated in the experiment shown in Table 11, which includes appropriate controls

TABLE 11—RESULTS OF FIXATION TESTS WITH SERUM FROM IMMUNIZED ANIMALS\*

Tube No	Rhus Antigen, c c	Immune Serum 56°, c c	c c	Hemolysis
1	"x"	1	No 19, 0 3 Alexin, 0 1	+ 25 minutes
2	"y"	1	No 10, 0 3 Alexin, 0 1	+ 15 minutes
3	"z"	1	No 19, 0 3 Alexin, 0 1	+ 15 minutes
4	"x"	1	Norm Rab 0 3 Alexin, 0 1	+ 25 minutes
5	"y"	1	Norm Rab 0 3 Alexin, 0 1	+ 15 minutes
6	"z"	1	Norm Rab 0 3 Alexin, 0 1	+ 15 minutes
7	Saline	1	No 19, 0 3 Alexin, 0 1	+ 15 minutes
8	"x"	1	Saline 0 3 Saline 0 1	0
9	"y"	1	Saline 0 3 Saline 0 1	0
10	"z"	1	Saline 0 3 Saline 0 1	0
11	"x"	1	No 15, 0 3 Alexin, 0 1	+ 15 minutes
12	"y"	1	No 15, 0 3 Alexin, 0 1	+ 15 minutes
13	"z"	1	No 15, 0 3 Alexin, 0 1	+ 15 minutes
14	"x"	1	No 13, 0 3 Alexin, 0 1	+ 18 hours
15	"y"	1	No 13, 0 3 Alexin, 0 1	+ 1 hr 15 min
16	"z"	1	No 13, 0 3 Alexin, 0 1	+ 1 hour
17	Saline	1	No 15, 0 3 Alexin, 0 1	+ 15 minutes
18	Saline	1	No 13, 0 3 Alexin, 0 1	+ 1 hour

\*Incubated 37° one hour, then added to each tube 1 c c 5 per cent saline suspension sheep corpuscles, sensitized, incubated 1½ hours

Note Antigen=Suspension of *Rhus diversiloba* toxin in normal saline, made from saturated alcoholic solution of toxin, in following proportions

"x"=5 per cent saturated alcoholic solution with normal saline

"y"=5 per cent saturated alcoholic solution with normal saline

"z"=0.5 per cent saturated alcoholic solution with normal saline

Alexin=Normal guinea-pig serum, 18 hours old, 10 per cent in normal saline

It is seen that these hemolytic tests failed to demonstrate the presence of antibodies by the Bordet-Gengou method in the sera of rabbits that had received repeated doses of the toxin. *The conclusion suggested is that attempts to demonstrate antibodies in rabbits treated with rhus toxin are futile.* This does not exclude the possibility of tissue immunity. Nevertheless, contrary to the reported experience of others, I am still as sensitive to poison oak as ever, though I have been severely poisoned, accidentally, on many occasions, and have poisoned limited areas experimentally a great many times.

#### THERAPEUTIC TESTS

In addition to the above investigations into the nature and action of the toxin, some observations and experiments were made testing therapeutic and prophylactic measures. Two methods were employed in studying therapy, some persons were poisoned in the usual accidental way by exposure to the plant in the country, and in other cases the dermatitis



was purposely induced<sup>9</sup> by applying the toxin, either pure or in some menstruum. The latter method is preferred because symmetrical spots can be chosen, and the usual variables in individuals eliminated. In cases of accidental poisoning the worse half of the body was selected for testing the therapeutic agent, the milder half being used for control. The prophylactic measures were tried on myself. The clinical observations detailed below serve to illustrate the methods employed, and to indicate the value of some treatments.

### IMMUNE'S SERUM

While it is recognized that a person, though immune, might not yield antitoxin in his serum, still, in connection with the previous experiments in animal immunity, it was thought worth while to test therapeutically the serum of a person who shows marked resistance to the toxin. Blood was therefore taken from the "Immune" heretofore referred to as "E. F." Experiment 10

#### *Experiment 13 —*

Test 1. A mixture of equal parts of water, tincture rhus, and blood from E. F., an immune, was applied to my arm and knee. Dermatitis developed at each place.

Test 2. A mixture of equal parts of E. F.'s blood and tincture rhus was applied to my arm. Dermatitis developed.

Test 3. Having smeared E. F.'s blood on my arm, tincture of rhus was then applied on the same area. Dermatitis resulted.

From these tests it appears that blood from an immune contains nothing able to inhibit the toxicity of rhus.

*Experiment 14 (Ammonia Water)* — Equal parts of ammonia and tincture rhus were mixed and tested on the skin. The mixture is toxic, from which it is evident that ammonia does not destroy the poison.

*Experiment 15 (Peroxid of Hydrogen)* — Because it is a strong oxidizer, it was presumed that hydrogen peroxid would have some curative property. But when tested by adding it in equal quantity to the rhus tincture, it failed to inhibit the toxicity, and when tested, with control, on a patch of dermatitis it was found inert.

*Experiment 16 (Aristol)* — The left of two artificial patches of dermatitis was treated during five days with a solution of aristol in cotton-seed oil. The control received no treatment. Both were scratched. Result. The *untreated* patch recovered first.

*Experiment 17* — The same test was made on the left of two spots produced by green leaves. The aristol in oil was applied five times in four days and protected by gauze held in place by plaster. Result. No difference could be noted. Aristol therefore appears to be of no value.

*Experiment 18 (Castor Oil)* — A mixture of equal parts of 10 per cent tincture of rhus and castor oil was rubbed on the arm. In thirty-six hours there was a slight itching, but no eruption.

*Experiment 19 (Cedar Oil)* — A similar mixture with cedar oil was applied to the arm. After thirty-six hours, a slight eruption appeared which later developed into a fair patch of itching dermatitis.

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<sup>9</sup> In all human skin tests the author was the subject, except where otherwise mentioned, and the toxin always from *Rhus diversiloba*, except where otherwise stated.

*Experiment 20 (Cotton Seed Oil)* —A similar mixture with cotton seed oil was applied to the thin skin at the wrist. After eight days no dermatitis had appeared.

*Experiment 21* —Cotton seed oil in which green leaves had been soaked for twenty-four hours was applied to the arm. The result was a slight dermatitis. This, repeated on another person, gave the same result.

*Experiment 22* —Some cotton seed oil in which green leaves had been heated was applied to the arm. After four days, itching began, and in five days, a slight eruption.

*Experiment 23* —A mixture of equal parts of tincture of rhus and cotton seed oil was applied to the arm. No dermatitis was detected in eight days.

These results raised the question whether cotton-seed oil did not combine chemically with the toxin, destroying the toxicity. To test this point, the mixture of oil and tincture was allowed to stand a few days when the tincture formed a layer above the oil. This supernatant fluid was toxic, producing dermatitis.

*Experiment 24* —A mixture of equal parts of tincture rhus and of tincture of green soap was applied to the arm and protected by gauze. After twenty-four hours only a slight eruption was noted.

*Experiment 25* —A mixture of tincture of rhus, 25 parts, and tincture of green soap, 5 parts, was applied to arm and protected with gauze. Only slight dermatitis resulted.

*Experiment 26* —After allowing tincture of green soap to dry on a spot, tincture of rhus was applied. A control spot was made with the rhus alone. Both spots were protected with gauze. The control took well, while the soaped spot showed a slight dermatitis. Thus it appears that soap deters the poison of rhus.

*Experiment 27 (Ichthyol Collodion)* —The worse of two patches of dermatitis, three days old, was painted with a 5 per cent ichthyol collodion daily. In twenty-four hours distinct improvement was noted in the treated patch, and this patch recovered earlier. This was confirmed in treating hospital cases.

*Experiment 28 (Hyposulphate of Sodium)* —Tests with this substance were also negative. It failed to inhibit the toxicity when added in large proportion to the tincture of rhus, and it failed to show curative effect on dermatitis patches compared with controls.

*Experiment 29 (Iodid of Potassium)* —This substance in strong solution, added to an equal part of tincture rhus, failed to inhibit the toxicity as tested on the skin.

*Experiment 30 (Tincture of Iodin)* —Full official strength tincture of iodine when mixed with an equal quantity of tincture of rhus *destroys the poison*, for when this mixture is tested on my arm no dermatitis results. If, however, the strength is reduced to less than 5 per cent of the mixture, by addition of water or alcohol, the toxicity is not destroyed completely.

*Experiment 31* —Tincture of iodine also has curative property. To one of two patches of dermatitis, official tincture of iodine was applied. The application burned. But the treated patch recovered earlier than the control. Itching quickly subsided and healing followed. The spot remained discolored, and tender, presumably from iodine burning.

*Experiment 32* —The right of two patches of dermatitis was rubbed with 90 drops of water mixed with 10 drops of tincture of iodine. The control was rubbed with alcohol. The application of iodine caused a burning sensation, not severe. In twenty-four hours the rhus dermatitis had disappeared, but was replaced by an iodine burn. The control ran a normal course.

*Experiment 33 (Potassium Permanganate)*—A mixture of equal parts of potassium permanganate (0.50 gm in 120 cc) with tincture rhus, when tested on the arm was found to be absolutely non-toxic

*Experiment 34*—One of two patches of dermatitis was painted with potassium permanganate in the above strength. The treated patch healed earlier than the control

*Experiment 35 (Magnesium Sulphate)*—Chemical Tests. A fresh rhus leaf macerated with a saturated solution of magnesium sulphate remained toxic, as proven by testing on my arm

*Experiment 36*—Saturated solution of magnesium sulphate (Squibb's), added in equal quantity to tincture rhus, does not inhibit the toxicity, for dermatitis results when the mixture is applied to the skin

### THERAPEUTIC TESTS

Though magnesium sulphate fails to destroy the toxicity of rhus when mixed with its tincture, or its juice, it nevertheless possesses definite therapeutic value

*Experiment 37—Test 1*. In one of two patches of dermatitis, saturated solution of magnesium sulphate was rubbed three times at hour intervals. By the next morning the treated patch was better than the control. Three more similar applications were made during the forenoon and by noon a very marked improvement was noted. The treated patch recovered earlier than the control

*Test 2*. To one of two patches of dermatitis, saturated solution of magnesium sulphate (Squibb's) was applied on gauze, covered with rubber tissue, and a bandage. A similar dressing was applied to the control, using water in place of magnesium. After twenty-four hours, while the first patch was not healed, it was free from itching, was not tender, and not edematous, thus contrasting with the control, which remained tender for six days

### HOSPITAL CASES

A B, male, aged 23, was poisoned four days previously. Whole face was edematous and the right eye closed. On Oct 25, 1911, in the afternoon, hot applications of 2 per cent permanganate were begun, but applied only to the right side of the face. In thirty hours the right eye was in good condition. The left side recovered tardily

B C, male, March, 1912, face and hands severely poisoned. The right side of the face and the right arm were treated with the hot permanganate, while the opposite side was treated with hot standard photographer's solution of sodium hyposulphite. In addition, both arms were bandaged in their respective solutions. After twenty-four hours the patient stated that the permanganate side felt distinctly better than the other. The right side recovered the earlier

E U, male, aged 25, was poisoned four days previously. Both arms showed marked edema, vesicles and pustules. He had already applied cold permanganate six or seven times. Hot permanganate was applied frequently by the nurse. There was no improvement in forty-eight hours. When the solution was changed to hot mercuric chlorid, and bandaging begun with the same, recovery began

This case illustrates the uselessness of permanganate when the vesicles become infected

A E, male, aged 45. Dermatitis one day old. The whole face was swollen. The eyes half closed by edema of both lids. The right ear was much swollen. Thirty hours after the dermatitis began, hot permanganate saturated solution was applied to all areas. The application burned severely, especially the eyelids. Recovery occurred in five days, though this man had always been two weeks getting well. A weaker solution of permanganate would have been better

There are two objections to the use of potassium permanganate. It produces a mahogany brown stain, at times difficult to remove. However, a 1 per cent. solution of oxalic acid is usually sufficient to disperse the stain. It should not be forgotten that this acid, internally, is a violent poison, and should be used with great caution. The other objection is that after its use, followed by oxalic acid, the skin is left severely cracked, which is especially disagreeable on the face and hands. This is met by soothing ointments or oils.

#### PROPHYLAXIS

I have frequently protected myself against poisoning, as have others, when not in direct contact with the plant, by simply washing the exposed surfaces within a few hours after exposure, using soap and hot water. When, however, I am to be thoroughly exposed, as in gathering the leaves or handling the dried plants, I prefer the protection of cotton-seed oil on hands, arms and face, gloves, a bath for the whole body as soon after exposure as possible, and a change of clothing.

#### TREATMENT

Inasmuch as the poison, after alighting on the skin, takes some time to penetrate, the first thing to do is to prevent penetration by a soap and hot-water bath of the whole body, including the hair. No article of clothing should be donned that has been exposed to the poison. Itching is readily relieved by water as hot as can be borne, and is usually a pleasant treatment, and of itself assists cure. The remedies previously discussed may then be used. If pustules have formed, the condition of bacterial infection must be recognized and will alter treatment, as illustrated by hospital case, E U.

#### CONCLUSIONS

The toxic principle of rhus, while non-volatile, can poison at a distance by means of mechanical carriers. It is not destroyed by subjection for one hour to 100 C, and is carried, potent, by the smoke from burning rhus plants. The dermatitis is purely a local affection, and is not spread by the blood or lymph, or by the serum of the blebs. The sweat reaction has no relation to susceptibility. Absolute immunity in man is improbable, and experimental immunity in animals is not yet demonstrated. A permanent aqueous suspension of the alcoholic solution of the toxin can be prepared and remains toxic, this is precipitated by salt. As much as 0.025 gm. toxin can be given intravenously in aqueous suspension to a 2,000 gm. rabbit without fatal effect, and as much as 0.03875 gm. can be given to a 280 gm. guinea-pig subcutaneously without fatal effect.

Inasmuch as animals cannot be killed by the pure toxin, it is impossible to demonstrate antitoxic effect by the serum of animals that have received repeated doses of the toxin. The Bordet-Gengou fixation reaction failed to demonstrate the presence of antibodies in the sera of animals so treated.

The simplest prophylactic measure against rhus poisoning is to wash well with soap and hot water as soon after exposure as possible. The protection of the skin by anointing with cotton-seed oil before exposure, and washing this off within a few hours with soap and water, renders prophylaxis fairly certain. The following remedies have therapeutic value: hot water, ichthyol collodion, potassium permanganate, magnesium sulphate and tincture of iodine.

I gladly acknowledge my lasting obligation to Dr. F. P. Gay, Dr. G. Y. Rusk, and Dr. Chas. B. Bennett of the University of California for their valuable advice and help.

# EXPERIMENTAL EOSINOPHILIA WITH AN EXTRACT OF AN ANIMAL PARASITE

ITS RELATION TO ANAPHYLAXIS AND CERTAIN CLINICAL PROBLEMS

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NEW YORK

The functions of the eosinophil cells remain one of the mysteries of biology. Our knowledge of these cells includes their morphology, their place of origin and the naming of the various clinical conditions in which their number either in circulating blood or locally in the tissues varies from the usual. Of the rôle played by the eosinophil leukocytes in the economy of the body we know little. Experimental work has lagged far behind speculation in this field.

Some months ago a phase of the problem of the functions of the eosinophil cells was suggested by two observations. In 1910 a case of bronchial asthma came to my notice showing extreme blood-changes—a leukocytosis of 56,000, an eosinophilia of 77 per cent<sup>1</sup>. This was placed on record together with a review of the literature of this well-known feature of asthma. At about the same time Goldschmidt<sup>2</sup> recorded the observation that laboratory workers whose duties led them to dissect *Ascarides* became sensitized so that tenderness and swelling of the fingers, conjunctivitis, coryza, sneezing, cough and asthmatic attacks resulted, and became increasingly severe with repeated handling of the material. It was found that the asthmatic attacks had a remarkable periodicity and in some instances persisted two weeks after cessation of contact with the worms.

Several baffling problems are linked, however complexly, by these observations. Common to both bronchial asthma and *Ascaris* infestation is an increase of the eosinophils of the blood. One may well ask the significance of the eosinophilia in this association. Further, it has been suggested that asthma may be classified among the phenomena of anaphylaxis<sup>3</sup>. Many of the reflex and toxic symptoms seen clinically in

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\*From the Department of Practice of Medicine College of Physicians and Surgeons, Columbia University

1 Herrick, W W. The Eosinophilia of Bronchial Asthma, with Report of a Case Showing Extreme Blood Changes. Jour Am Med Assn, 1911, lvi, 1836

2 Goldschmidt. Die Ascarisvergiftung. Munchen med Wehnschr, 1910, lvi, 1991

3 Meltzer. Bronchial Asthma as a Phenomenon of Anaphylaxis. Jour Am Med Assn, 1910, lv, 12, 1020

*Ascaris* infestation have been assigned to the same category<sup>4</sup> Is, then, the eosinophilia of the blood present in most instances of either of these conditions the result of specific sensitization or anaphylaxis? If this eosinophilia can be explained on such a basis, exactly what are the substances responsible for this effect and under what conditions is such effect produced?

As such a study involves of necessity experimental eosinophilia with animal parasites or their products, it may be well to review the subject briefly

#### REVIEW OF LITERATURE

Calamida<sup>5</sup> prepared from the *Tenia cucumerina* and the *Tenia coe-nurus* of the dog a concentrated extract which he claims has a chemotactic effect on the eosinophils. A capillary tube containing this extract placed in the peritoneal cavities and subcutaneous tissues of rabbits was found at the end of twenty-four hours to contain many leukocytes, most of which were eosinophils. The most thorough study of the eosinophil leukocytes is that made by Opie<sup>6</sup> in 1904. Working with guinea-pigs, Opie produced trichiniasis by feeding infected meat and noted a striking rise in number of eosinophil cells in the blood at the end of the second week after infection. This eosinophilia reached its maximum at the end of the third week. In the lungs and mesenteric glands of the infected animals, masses of eosinophil cells were observed replacing polymorpho-nuclear neutrophils and resembling small abscesses. This increase in the eosinophils was accompanied by characteristic changes in the bone-marrow—a diminution of fat and a replacement of this tissue by cellular elements, prominent among which were immense numbers of cells with eosinophil granulations, many showing mitoses. Opie is in accord with Ehrlich in the opinion that the bone-marrow is the seat of multiplication of the eosinophil leukocytes. Infection with a large number of *Trich-inellae* caused diminution in the number of eosinophils and was quickly fatal. In general, a mild infection seemed to stimulate the eosinophil cells to rapid multiplication, a severe infection caused their destruction. Opie noted a remarkable relation between the nutrition of the guinea-pigs and the numbers of eosinophils in the circulating blood. The animals below 500 gm in weight had an average eosinophilia of 2 per cent, those above this weight quite constantly a larger number of these cells. A

4 This has been suggested by Moschcowitz. *Eosinophilia and Anaphylaxis* New York Med Jour, 1910, xciii, 15, and others.

5 Calamida. *Weitere Untersuchungen über das Gift der Tamen*. Centralbl f. Bakter u. Parasit, 1901, xxx, 374.

6 Opie. *The Occurrence of Cells with Eosinophil Granulation and Their Relation to Nutrition*. Am Jour Med Sc, 1904, cxvii, 2, 217. also *An Experimental Study of the Relation of Cells with Eosinophil Granulations to Infection with an Animal Parasite*, *ibid*, 1904, cxvii, 3, 477.

periodic variation in the number of eosinophils was shown by many animals. Starvation caused prompt fall in the number of eosinophil leukocytes and with gain in weight their numbers again rose.

Proscher<sup>7</sup> produced local eosinophilia by the intraperitoneal injection of an extract of *Tenia solium*, finding that after an interval of five to forty minutes the polynuclear neutrophils in the peritoneal fluid about the site of injection were replaced by eosinophils. Proscher and Pappenheim<sup>8</sup> injected an extract of *Tenia saginata* into the veins of rabbits and noted a resulting eosinophilia of the blood. Staubli<sup>9</sup> has repeated a part of the work of Opie. This observer infected guinea-pigs with the *Trichinella spiralis* and noted the consequent eosinophilia after a period of eight days or more. He found that the eosinophil increase persisted as long as three and one-half years, that the eosinophil-producing substance did not traverse the placenta and that offspring of animals showing eosinophilia do not have this characteristic of their blood-picture. Staubli also showed the diminution of the number of these cells during the entire time the organism is under the influence of bacterial products and the existence of a reciprocal relationship between the eosinophil leukocytes and the polymorphonuclear neutrophils.

#### OBJECTS OF AUTHOR'S STUDY

The problems toward the solution of which I have attempted to contribute are as follows: 1. Whether eosinophilia of the blood could be produced experimentally by the use of an extract of *Ascaris lumbricoides*. 2. Under what conditions of administration of this extract such eosinophilia might be brought about. 3. Whether or not the substance influencing the eosinophils is a protein. 4. Whether such eosinophil increase bears any relation to specific sensitization or anaphylaxis. Throughout the work the possible relation of these questions to the clinical problem of bronchial asthma has been constantly in mind.

#### EXPERIMENTAL WORK

Guinea-pigs were chosen for the experiments, since the blood-cells of these animals resemble rather closely those of man in morphology and in reaction to bacterial and other agencies. For convenience the fine granular polymorphonuclear amphophils of the guinea-pig are termed polynuclears. It is important to have clearly in mind the usual blood-picture

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<sup>7</sup> Proscher. Ueber experimentelle Erzeugung von eosinophile Exsudaten. Fol. Haematol., 1905, 11, 543.

<sup>8</sup> Proscher and Pappenheim. Ueber experimentelle Leucocyten. Fol. Haematol., 1904, 1, 638.

<sup>9</sup> Staubli. Trichinosis, 1909, p. 107 et seq., also Die klinische Bedeutung der Eosinophilie, Ergebn. d. inn. Med. u. Kinder., 1910, vi, 12 and Ueber Eosinophilie, Samuel klin. Vortr., 1909, cxvii, 43.



of the guinea-pig Gulland and Goodall<sup>10</sup> give as an average the following count of leukocytes Number in a c mm, 10,500, polynuclears, 43 per cent, lymphocytes, 52 per cent, eosinophils, 2.5 per cent, basophils, 2.5 per cent Kuiloff, quoted by Opie from Ehrlich and Lazarus, states that the average percentage of eosinophils is 1 Kanthack and Hardy<sup>11</sup> give 2 per cent to 3 per cent as the average figures Opie's figures are higher In counts of 10 guinea-pigs the average percentage of eosinophil leukocytes was found to be 11 I have averaged the counts of seventeen animals before experiments were begun and find the following figures Leukocytes, 10,311, polynuclears, 34.5 per cent, large lymphocytes, 2.5 per cent, small lymphocytes, 59.5 per cent, eosinophils, 2.5 per cent, basophils, 1 per cent, total number of eosinophils in 1 c mm, 363 In making the counts recorded in this work the blood was taken from the ear, a pipet giving a dilution of 1 to 20 and the Zappert counting chamber were used Smears were made in the usual way, stained by Wright's stain, and 200 cells counted

The extract used was prepared from the *Ascaris lumbricoides* of the pig The fresh worms were washed in distilled water, finely divided, then ground with sand in a mortar and sufficient 0.5 per cent sodium chlorid solution added so that each c c of the decanted solution represented 1 gm of the fresh material The solution was passed through a Berkefeld filter and to it was added 0.5 per cent phenol, a preservative having on intraperitoneal injection no effect on the numbers of eosinophils or basophils of the guinea-pig (Schlecht<sup>12</sup>) This extract, kept on ice, was a slightly turbid yellowish liquid, having the acrid odor characteristic of the *Ascarides* and containing protein in considerable amount Injected intraperitoneally in guinea-pigs peritonitis did not follow, nor did any direct toxic effects result from the rather small quantities—2 to 5 c c—used It may be of interest to record that, notwithstanding having worked with *Ascarides* and their extracts at intervals for more than a year and a half, neither the laboratory *diener* nor myself has shown symptoms of sensitization

Taking up in their order the problems suggested, report is given of a selected number of such experiments with the fifty-six animals used as have bearing on their solution

There can be no question that increase in the eosinophils of the blood of guinea-pigs may be produced experimentally by the intraperitoneal

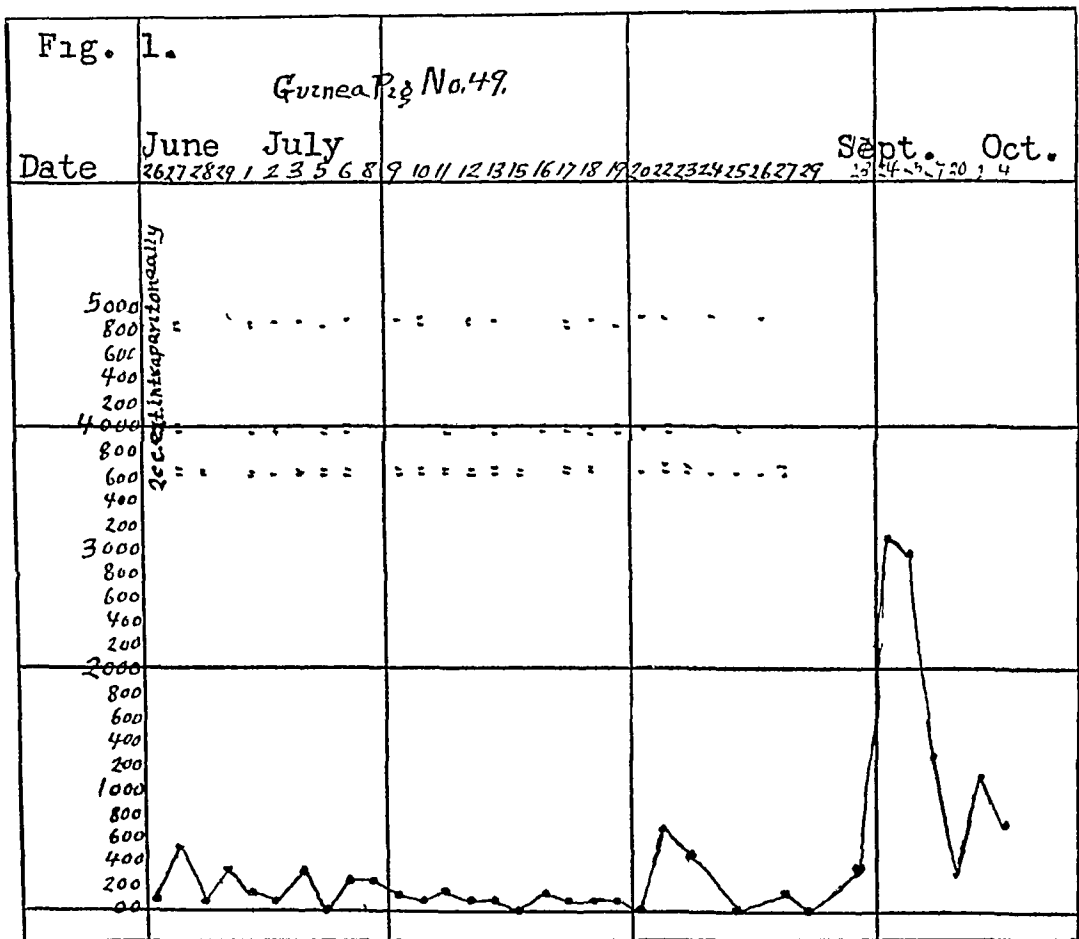
10 Gulland and Goodall The Blood, 1912, p 76

11 Kanthack and Hardy Wandering Cells of Mammalia Jour Physiol, London, 1894, xvii, 81

12 Schlecht Ueber die Einwirkung von Serum injectionen auf die Eosinophilen und Mastzellen des menschlichen und tierischen Blut Deutsch Archiv f klin Med, 1910, xcviii, 308

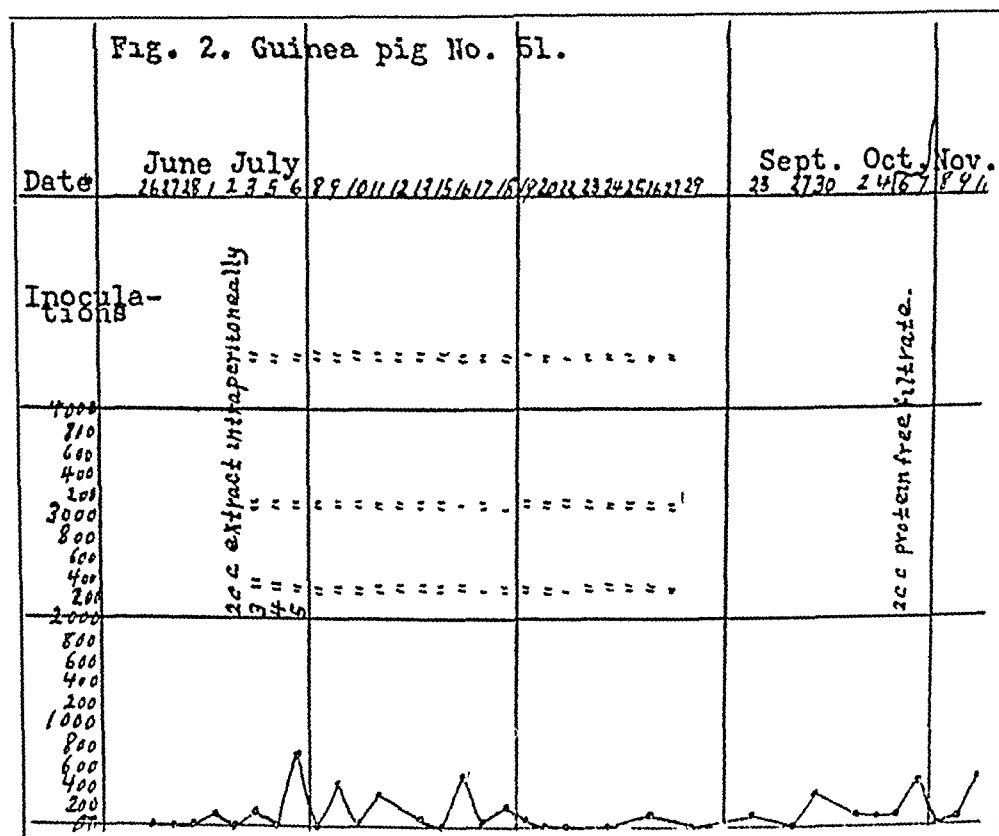
injection of an extract of *Ascaris lumbricoides*. In each instance in which this phase of the problem was investigated a positive result was obtained (Experiments with Guinea-Pigs 34, 36, 46, 47, 48, 49, 53)

The methods of administration of the extract bringing about such increase in the number of eosinophils are of particular interest. As to dosage, a comparatively small amount of material is effectual when introduced into the peritoneal space of guinea-pigs, 2 c c of the extract was used in all but a very few instances. Where larger amounts—never more than 5 c c—were employed this is noted on the charts. The larger amounts seemed not to influence results in any way differing from the



smaller dosage, the increase in number of eosinophils bearing no relation to the amount of extract administered. The factor of greatest influence in the production of this eosinophilia was the interval between injections of the extract. Injections of 2 to 5 c c daily over a period of four weeks was without influence on the eosinophil content of the blood of guinea-pigs (Fig 1, Guinea-Pig 49, and Fig 2, Guinea-Pig 51). Injections of 2 c c of the extract every second or every third day was also without result (Fig 3, Guinea-Pig 46). Two series of injections daily or every second or third day, the two series being separated by an interval of ten days, was accompanied during the second series by but slight rise in the

number of eosinophils (Fig 3, Guinea-Pig 46 ) Injections of the extract at intervals of five to twenty-five days was followed without exception by a striking increase in the eosinophils of the blood (Figs 4, 10, 6 and 9, Guinea-Pigs 45, 34, 47 and 53 ) A series of injections followed after an interval of two to eight weeks by a further single injection had as a sequel a striking increase in the number of eosinophils (Guinea-Pigs 36, 46 and 49 , Figs 7, 3 and 1 ) In no instance was a first injection followed by an eosinophil increase Each single reinjection when separated from the preceding by an interval of five days or more was followed by a more prompt response in the way of an eosinophil increase (Guinea-Pigs 34,

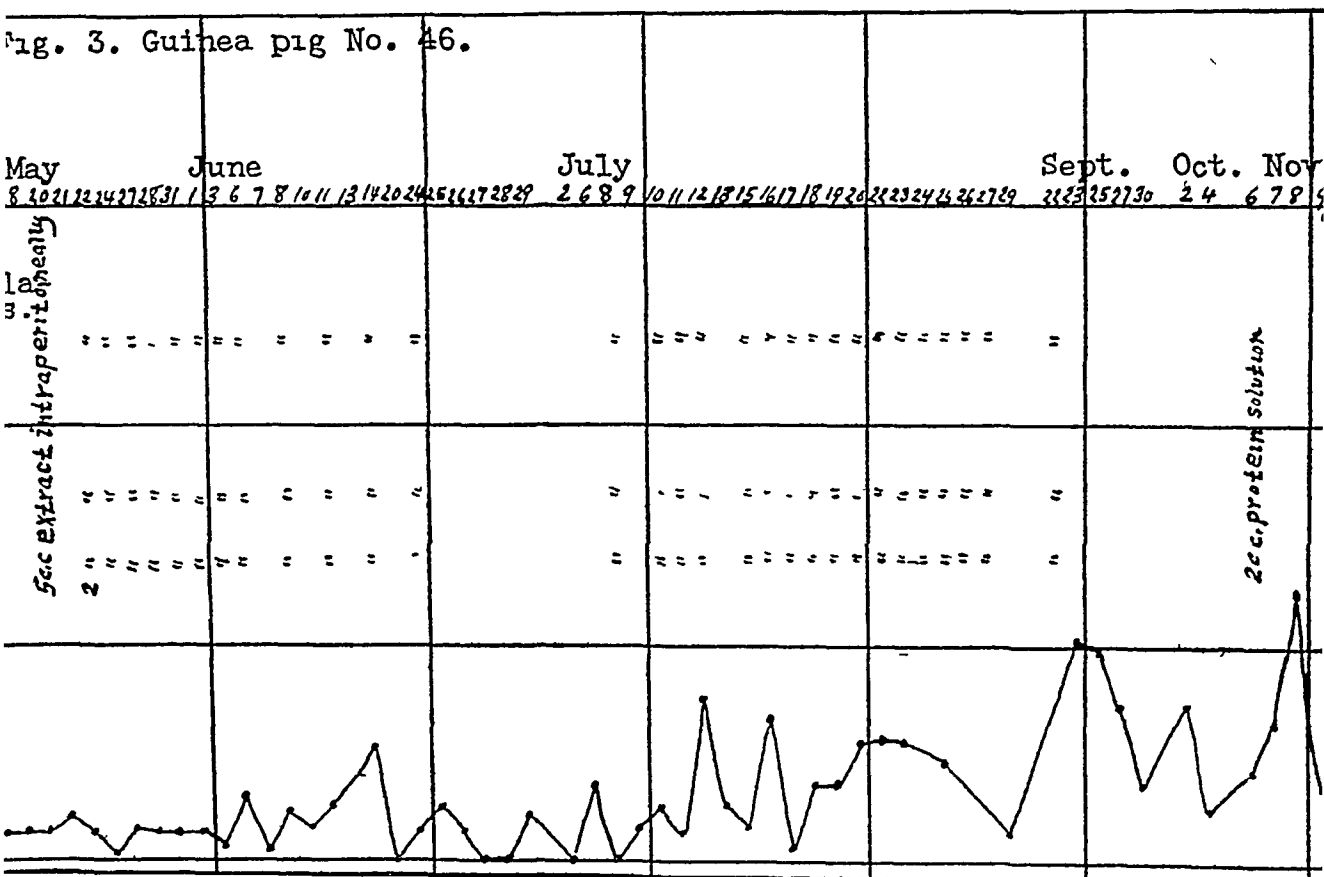


dose of 2 c c , became enormous, these cells reaching the extremely high figure of 5,172 in a c mm Explanation of the course of the eosinophil curve in this animal is difficult in that the rise in number of these cells was not so prompt an effect of the injections as in the case of the other animals, the charts of which are here given I have noted that guinea-pigs showing a high control count of eosinophils react to inoculations of extract of *Ascaris* in a manner less typical than that characterizing animals having a normal number of these cells.

#### NATURE OF THE SUBSTANCE PRODUCING EOSINOPHILIA

Is the substance influencing the eosinophil cells a protein?

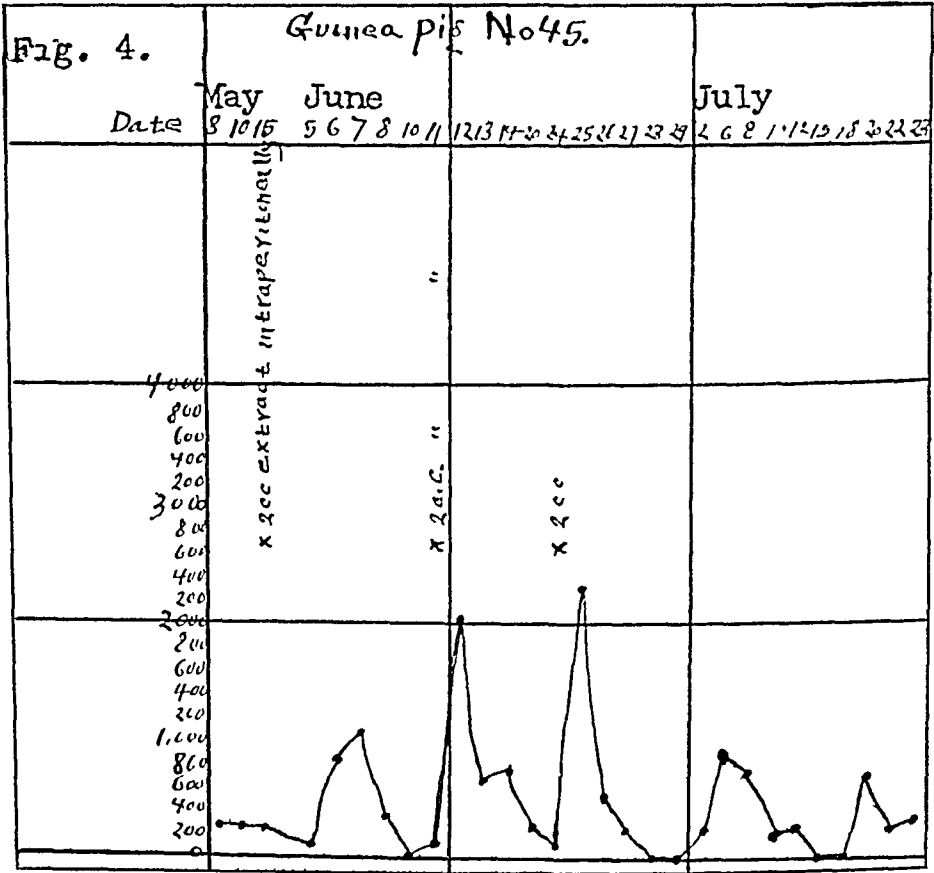
The original extract was rich in albumin, giving the biuret reaction, positive Heller's test and abundant precipitation on acidulation and



boiling The protein was precipitated by the addition of two volumes of acetone The abundant precipitate, isolated by filtration, was dried and dissolved in 0.5 per cent salt solution One gram of this precipitate was dissolved in 2 c c of the salt solution This amount was injected into the peritoneal cavities of guinea-pigs previously sensitized with the original extract, death from anaphylactic shock resulting in Guinea-Pig 50, while in Guinea-Pig 46 (Fig 3) and in Guinea-Pig 48 (Fig 8) prompt rise in the number of eosinophils followed Fractional precipitation of the

proteins of the extract after the method of Pick<sup>13</sup> was not done as the effect on the eosinophils of the intraperitoneal injection of many simple proteins has been studied by Schlecht, whose work is quoted below.

To secure an extract practically protein free, the original extract was acidulated with acetic acid and boiled, the resulting precipitate filtered through ordinary filter paper, or, in some cases, through infusorial earth and filter paper. The filtrate thus obtained gave a faint biuret reaction, but no coagulum on acidulation and heating. This filtrate injected into the peritoneal space of guinea-pigs previously sensitized with the original extract was without influence on the eosinophil cells of the blood.

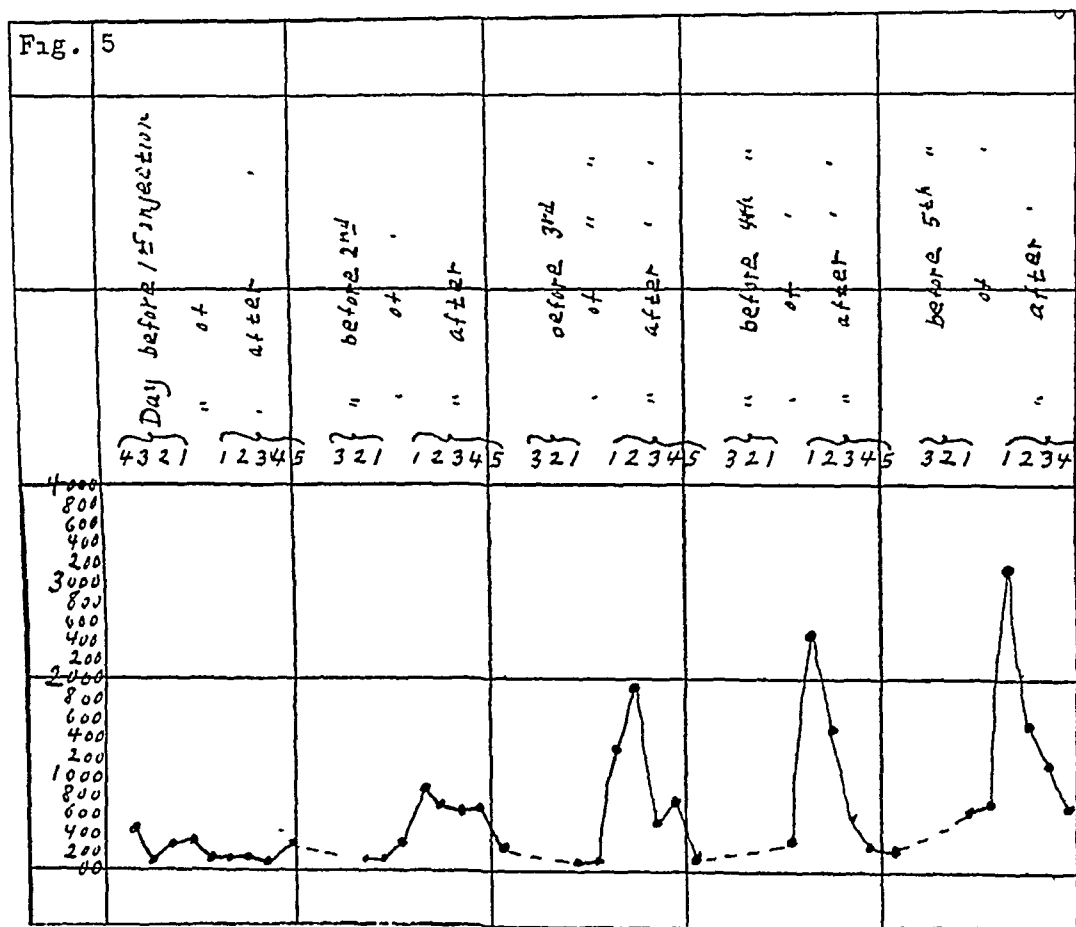


(Guinea-Pigs 46, 48 and 51) It may therefore be concluded that the protein of the *Ascaris* extract is the substance responsible for the eosinophil increase when administered by the above-described methods. This conclusion gains further proof from the work of Schlecht,<sup>14</sup> who, in a valuable contribution, has shown that the intraperitoneal injection of

13 Pick Zur Kenntniss der Immunkorper, Hofmeister's Beitrage, 1902, 1, 351

14 Schlecht Ueber die Einwirkung von Serum injectionen auf die Eosinophilen und Mastzellen des menschlichen und tierischen Blut Deutsch Arch f klin Med, 1910, xcviii, 308

alien protein is followed in guinea-pigs by a striking eosinophilia of the blood. This result was obtained by the injection of whole blood-serum, egg albumin, fibrin, serum-albumin, serum-globulin and hemi-albumose, but not peptone or the products of further protein digestion—the amino acids, etc. The results obtained in my experiments with the extract of *Ascaris lumbricoides* and with the isolated protein of this extract correspond in general with those reported by Schlecht from the use of simple proteins. There is the exception that Schlecht noted the eosinophil increase following injections at intervals of less than three days when such injections were continued for a number of days.

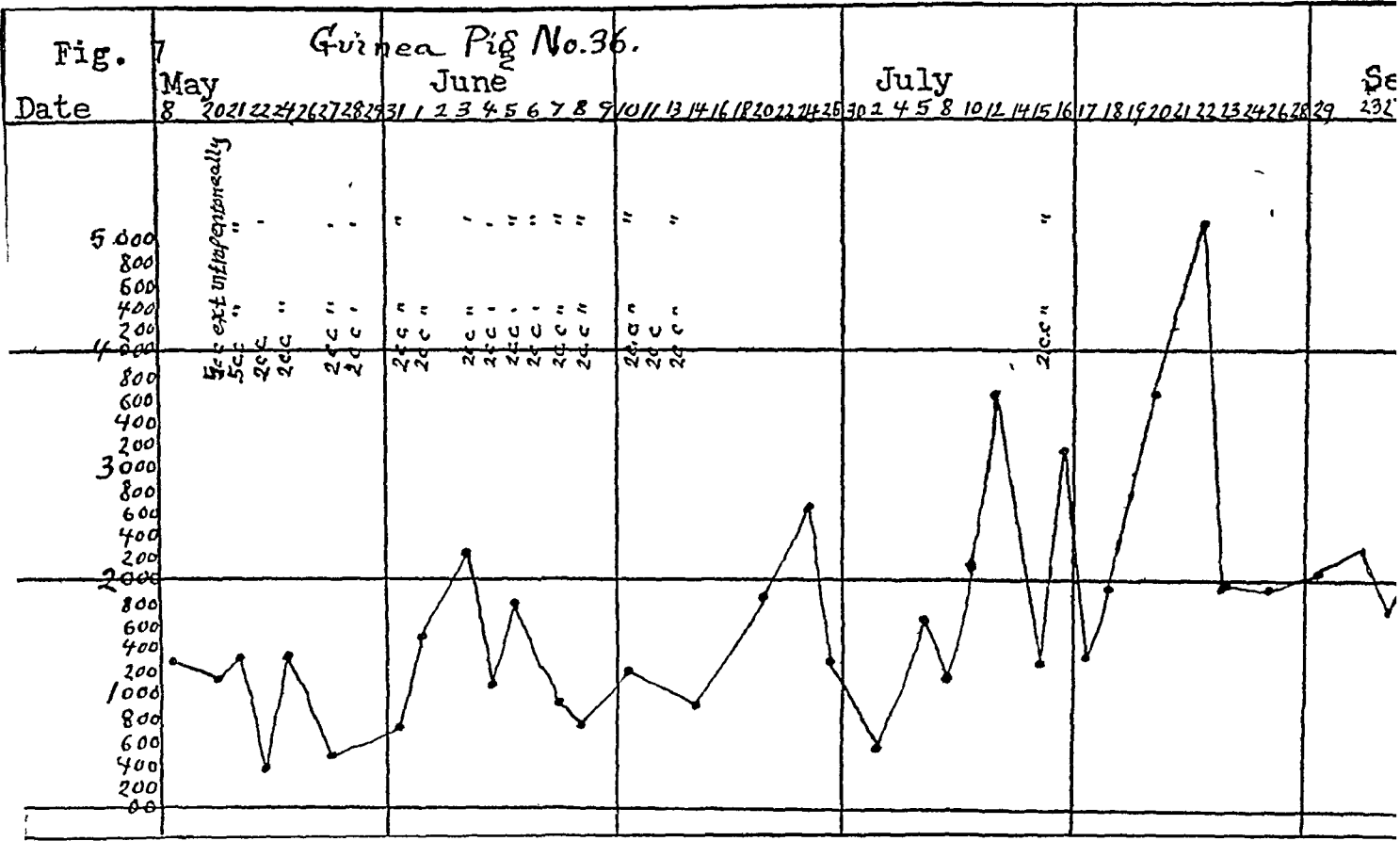


#### EOSINOPHILIA AND ANAPHYLAXIS

To the question, "What connection, if any, has the increase in number of the eosinophil cells of the blood noted in these experiments with anaphylaxis," no final answer can be given. However, some suggestive facts are brought out. In no instance observed did the eosinophil increase occur during a time when the animals could properly be judged immune, nor was any such increase noted during the anaphylactic shock. Immediately following the anaphylactic period the rise in eosinophils in the blood was marked and constant and more pronounced as the previous sensitization had been more thorough. Further injection of the extract



danger of the anaphylactic period Of interest in this connection is the further work of Schlecht<sup>15</sup> in showing that lungs of guinea-pigs dead from anaphylactic shock contain eosinophil cells in large numbers and that animals may be sensitized or may show local evidences of sensitization in the lungs by the inhalation of sprayed serum. The work of Schittenhelm, Weichardt and Grisshammer<sup>16</sup> claims attention in this relation These investigators studied the effect on the blood-cells of dogs of the intravenous injection of albumin, peptone and bacterial protein, finding an immediate leukopenia, the degree of which depended not on the amount of material injected, but on its kind Albumin injected in



sensitized animals caused a leukopenia lasting some hours and followed by a stage of leukocytosis which subsided after four to six days This leukocytosis was mostly of the polynuclear neutrophils, but as the leukocytosis began to decline the eosinophils reached high numbers

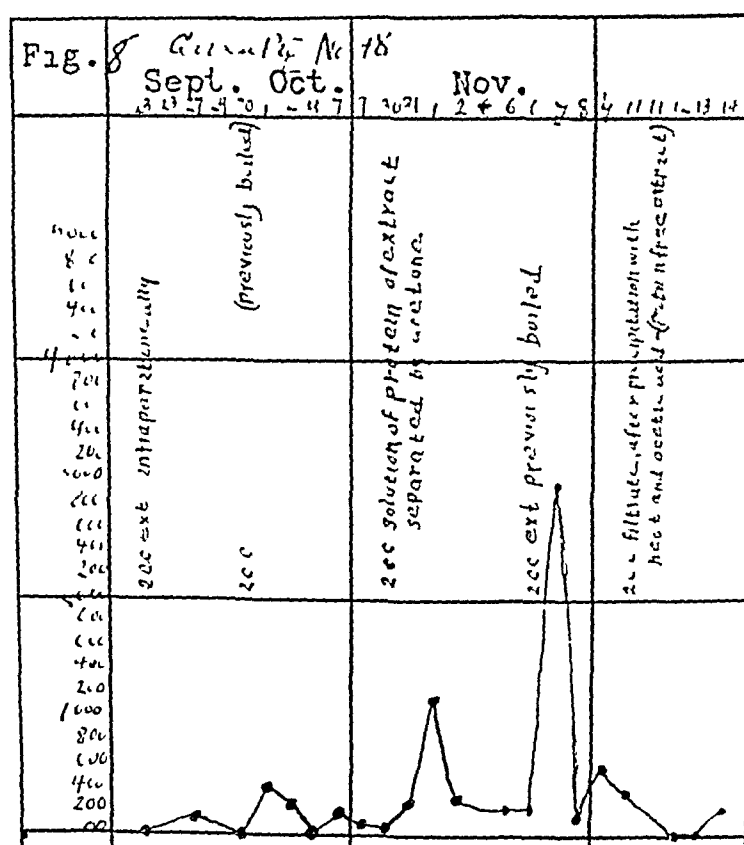
In so far as a single observation is of value, it appears that while the offspring of a sensitized animal are also sensitive to the specific protein employed, the capacity of responding by a hypereosinophilia on the injec-

15 Schlecht and Schwenker Ueber die Beziehungen der Eosinophilie zur Anaphylaxie Deutsch Arch f klin Med, 1912, cviii, 405  
16 Schittenhelm Weichardt and Grisshammer Eiweissumsatz und Ueberempfindlichkeit Ztschr f exper Path u Therap, 1912, x, 3, 412

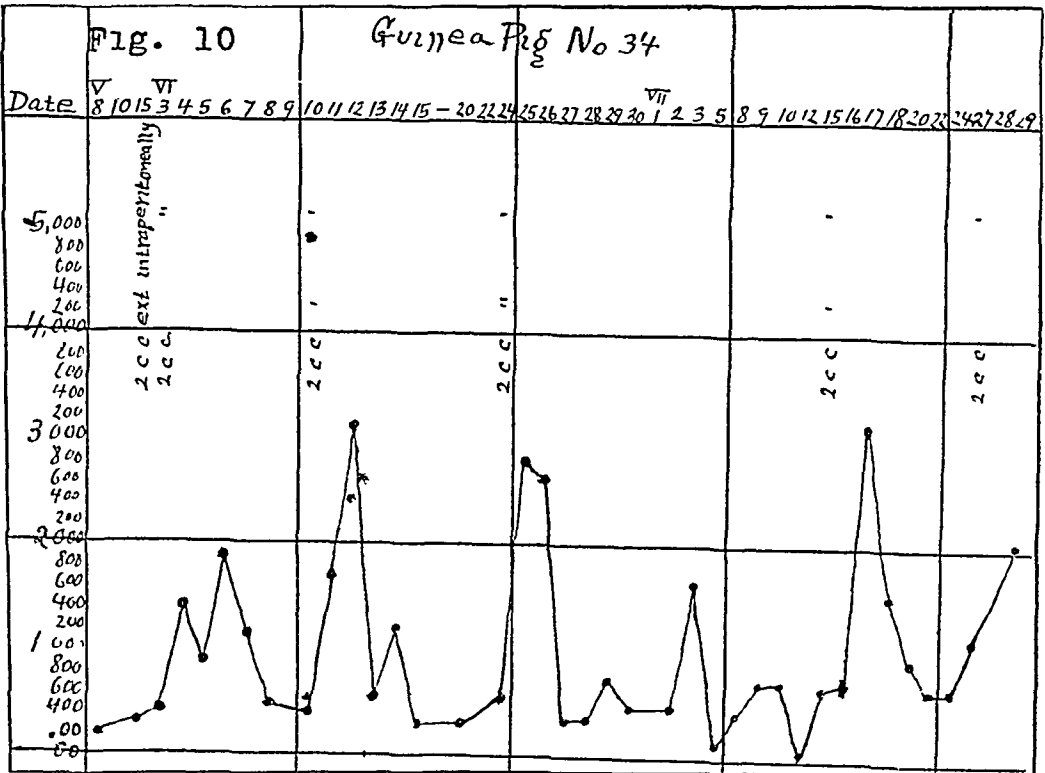
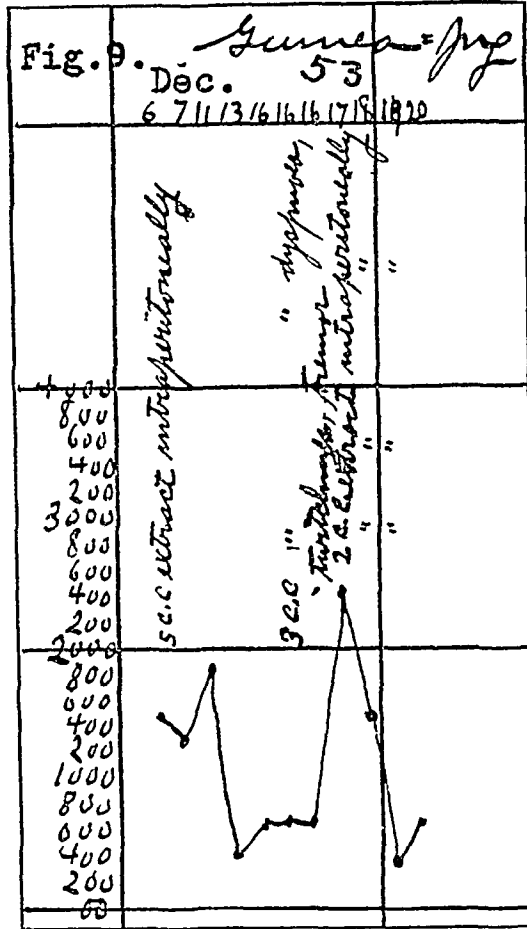


tion of the specific protein is not transmitted. That fact has an analogy in the observation of Staubli, already cited, that the eosinophil-producing substance present in experimental trichiniasis in guinea-pigs is not transmitted through the placenta.

From the evidence presented it appears justified to conclude that the eosinophilia accompanying infestation with animal parasites is the result of protein sensitization. Exactly how this sensitization is brought about is problematical. The specific protein material may be secreted by the parasites or may be absorbed from the disintegration of those parasites perishing within the alimentary tract or in the circulation of the host.



The experimental finding that administration of an extract of *Ascaris lumbricoides* at intervals of less than five days is not followed by increase in the number of eosinophils in the blood is difficult to reconcile with clinical conditions that may reasonably be assumed to obtain in infestation with these parasites where absorption of foreign material is probably more or less continuous. Undoubtedly there are factors of which we are as yet ignorant. That a considerable latent period is necessary between the time of infection and the development of the consequent eosinophilia is apparent. This is suggested by the observations of Opie and of Staubli, already quoted. Both found that increase in number of eosinophil leukocytes in the blood of guinea-pigs fed on meat containing



embryos of *Trichinella spiralis* took place only after lapse of eight or more days, at a time when the embryos were migrating from the intestine to their resting places in muscle or other tissue

It is tempting to conclude that hyper eosinophilia is the result of sensitization to alien protein. This would bring into line the increase in number of these cells following injections of tuberculin, in serum sickness, many food poisonings, hay fever, the eosinophilia noted about animal parasites and other foreign protein material. Granting this, one is lured a step further to seek in sensitization to protein a cause of many types of bronchial asthma. It may be that in the discovery of some substance capable of influencing the eosinophil cells of the body we may find the key to that important clinical secret—the control of bronchial asthma.

#### PROTOCOLS

GUINEA-PIG 6—May 27 Eosinophils 00 May 29, 1 cc extract *Ascaris* injected intraperitoneally May 30, leukocytes 6,400, eosinophils, 00 June 6, leukocytes, 8,000, eosinophils, 00 June 9, 2 cc extract injected intraperitoneally, followed in ten seconds by clonic convulsions. During convulsions, leukocytes 4,000, polynuclears, 47 per cent, mononuclears, 52.5 per cent, eosinophils, 0.5 per cent. Partial recovery for several hours, death after six hours.

GUINEA-PIG 49—Two cc extract of *Ascaris lumbricoides* injected intraperitoneally daily from June 26 to July 27 with no significant change in the eosinophil content of the blood. No injections given from July 27 to September 23, when an injection of 2 cc of the extract intraperitoneally gave in twenty-four hours an increase of the eosinophils from 360 to 3,040 per mm. No symptoms of anaphylactic shock.

GUINEA-PIG 51—Weight, 417 grams. Two cc original extract given July 1, 3 cc July 3, 4 cc July 5, 5 cc July 6 and almost daily thereafter, with an occasional day excepted, until July 27. No change in number of eosinophils noted. November 6, 2 cc of filtrate after precipitation of albumin of original extract given intraperitoneally. (This precipitation was made by heat and acidulation with acetic acid.) No change of note in the eosinophils resulted. No signs of anaphylaxis.

GUINEA-PIG 46—Weight, 340 grams. Five cc original extract given intraperitoneally May 20, 2 cc May 22 and on approximately alternate days thereafter to June 15. Then a single injection after ten days without effect on the number of eosinophils. July 8 to 29 injections of 2 cc were given daily or on alternate days with slight increase of the eosinophils. September 22, 2 cc extract given intraperitoneally, September 23, eosinophils, 2,010, September 30, 770.

November 6, 2 cc solution of protein in 0.5 per cent sodium chloride precipitated by acetone was given and was followed by an eosinophil increase from 860 to 1,360 in twenty-four hours, 2,511 in forty-eight hours. After seventy-two hours, eosinophils were 760. November 11, 2 cc filtrate of extract after coagulation of albumen with heat and acetic acid injected intraperitoneally without effect on eosinophils.

GUINEA-PIG 45—Weight, 320 grams. Two cc extract intraperitoneally May 15. Slight reduction in the number of eosinophils in the blood followed June 5, 4 cc extract given intraperitoneally. Severe anaphylactic shock after twenty minutes, dyspnea, cyanosis, convulsive movements, paralysis. The peripheral circulation was so affected during the shock that satisfactory specimens of blood could not be obtained. Recovery in twenty-four hours, when eosins

were 820 in a c mm In forty-eight hours eosins rose to 1,035, in ninety-six hours 400 per mm Third injection of the extract June 11, when eosins were 108 in a c mm In twenty-four hours eosins rose to 2,030, in ninety-six hours fell to 300 June 24 eosins numbered 110 A fourth injection of original extract given on this date was followed in twenty-four hours by eosinophil increase to 2,378 In forty-eight hours eosins numbered 536

GUINEA-PIG 50—Weight, 245 grams Control count of eosinophils 62 in 1 mm September 23, 2 c c extract injected intraperitoneally No change noted in number of eosinophils October 30, 2 c c solution in 0.5 per cent sodium chlorid of proteins of *Ascaris* extract injected intraperitoneally Death in forty-five minutes from respiratory paralysis

GUINEA-PIG 47—Weight, 485 grams Control counts of eosinophils showed variations from 0 to 438 per mm, 2 c c extract injected July 5, repeated July 10 Eosinophils rose from 153 to 762 in forty-eight hours after second injection, returning to 116 per mm the fifth day Injection repeated July 18 Eosinophils rose from 0 to 1,817 in forty-eight hours A fourth injection July 24 was followed in forty-eight hours by increase of the eosinophils from 504 to 2,548 per mm In each instance the eosinophilia subsided forty-eight hours after its maximum No evidences of anaphylactic shock

GUINEA-PIG 36—Weight, 460 grams Control counts showed high eosinophilia—above 1,000 per mm, 5 c c extract of *Ascaris* given for two days, then 2 c c daily or on alternate days from May 22 to June 13 with no change in the average number of eosinophils July 15 a single injection of 2 c c of the original extract was followed by an eosinophil increase to 3,160, which after four days reached 5,172 Previous to the last injection the eosinophils on July 12 rose to 3,618, without relation to any known factor November 6 an injection of 2 c c of previously boiled extract was followed by no change in number of eosinophils, which in this animal continued to be high

GUINEA-PIG 48—Weight, 260 grams, 2 c c extract given September 23, no change in eosinophils followed September 30, 2 c c of the extract previously boiled given intraperitoneally and followed in twenty-four hours by a rise in eosinophils from 0 to 395 per c mm October 30, 1.5 c c of a solution in normal salt solution of the proteins of the extract of *Ascaris* precipitated by acetone was given and followed in twenty-four hours by an eosinophilia of 1,188 from one of 280 November 6, 2 c c of the original extract previously boiled was injected and caused an increase in eosinophils from 200 to 2,952 November 11, 2 c c filtrate after precipitation of albumin by heat and acetic acid was injected and was followed by no rise in the number of eosinophils, rather was there a diminution in the number of these cells—from 330 to 55 in 1 mm No symptoms of anaphylactic shock

GUINEA-PIG 53—Male, weight, 675 grams Control count showed moderately high eosinophil count, 1,456 per c mm December 6, 5 c c regular extract given intraperitoneally No marked effect on eosinophils December 16 these cells numbered 612 per mm Three c c extract injected intraperitoneally on this date After fifteen minutes dyspnea, tremor, slight convulsive movements December 17, eosinophils 2,400 Two c c extract injected on same day December 18, eosinophils 1,416 Two c c extract given December 19, eosinophils 336 Two c c extract injected December 20, eosinophils 658

GUINEA-PIG 55—Male, weight, 260 grams, 2 months old, offspring of guinea-pig 45 (Fig 4) Born Oct 5, 1912 December 19, eosinophils 00 December 20, eosinophils 68 Five c c extract injected intraperitoneally After ten minutes dyspnea, convulsions, weakness of extremities, death

GUINEA-PIG 56—Male, weight, 350 grams Of same litter as No 55 December 18, eosinophils 80, 2.5 c c extract injected intraperitoneally, no signs of anaphylaxis December 19, eosinophils, 0, December 20, 0

GUINIA-PIG 34—Weight, 600 grams Two cc extract given intraperitoneally May 15, repeated June 3 and four times additionally at intervals of one, two, three and two weeks, successively Each injection after the first was followed by prompt rise in the number of eosinophils from 400 to 800 or to 3,192, as a maximum In the later injections the maximal eosinophilia occurred after twenty four hours

### CONCLUSIONS

1 A notable eosinophilia of the blood can be developed by the intraperitoneal injection of an aqueous extract of *Ascaris lumbricoides*

2 The substance causing such eosinophil increase is a protein

3 Previous sensitization is necessary to the development of this eosinophilia

4 It is impossible to produce such eosinophilia while the animals are immune to the extract

5 This eosinophilia may therefore be considered evidence of previous sensitization

6 There is a possible association of these facts with the problem of bronchial asthma

50 East Fifty-Third Street

TABLE 1—BLOOD-COUNTS IN GUINEA-PIG 49

Date	No Leuko- cytes	Per Cent Polynu- clears	Per Cent Large Lymph	Per Cent Small Lymph	Per Cent Baso- phils	Per Cent Eosin- ophils	No of Eosin- ophils
June 26	9,000	47	5	45	2	1	90*
27	7,840	19.5	2	70.5	1.5	6.5	510*
28	7,200	24	3	71	1	1	72*
29	7,400	14	1	78.5	1.5	5	370*
July 1	15,800	18.5	1.5	77.5	1.5	1	158*
2	8,000	17.5	3.5	75	3	1	80*
3	9,000	17	1	76	2	4	360*
5	10,400	10.5	0.5	89	0	0	000*
6	10,400	24	1	73	0	2	208*
8	11,400	40.5	1.5	54	2	2	228*
9	5,600	18	1	78	2	1	56*
10	6,000	22	2	73.5	1	1.5	90*
11	8,200	32.5	3.5	60	2	2	164*
12	7,200	2.5	1.5	93.5	1.5	1	72*
13	8,000	13	1	85	0	1	80*
15	6,000	19	2	79	0	0	00*
16	7,600	23	1.5	64	0	1.5	114*
17	7,200	8	0.5	87.5	3	1	72*
18	8,200	13.5	1.5	82	2	1	82*
19	8,400	21.5	1	70	6.5	1	84*
20	11,800	19	1.5	78	1.5	0	00*
22	18,800	27	0	67	2	4	752*
23	8,400	26	1.5	64.5	2.5	5.5	462*
24							*
25	9,800	23	0	75	2	0	*
26							*
27	15,000	22.5	4	72.5	0	1	150*
29	6,800	26	3	71	0	0	000

TABLE 1—Continued

Date	No Leuko-cytes	Per Cent Polynu-clears	Per Cent Large Lymph	Per Cent Small Lymph	Per Cent Baso-phils	Per Cent Eosin-ophils	No of Eosin-ophils
Sept 23	12,000	64	2 5	30 5	00	3	360*
24	15,200	42	3	32	3	20	3,040
25	16,600	41 5	2	34 5	3 5	18 5	3,071
27	12,600	25 5	2 5	54 5	7 5	10	1,260
30	10,400	30	2	61	4	3	304
Oct 2	13,200	41	5	46	1	7	924
4	11,600	28 5	4	60 5	0 5	6 5	744

\*Two c c of original extract given intraperitoneally in each instance

TABLE 2—BLOOD-COUNTS IN GUINEA-PIG 51

Date	No Leuko-cytes	Per Cent Polynu-clears	Per Cent Large Lymph	Per Cent Small Lymph	Per Cent Baso-phils	Per Cent Eosin-ophils	No of Eosin-ophils
June 26	5,000	13 5	0 5	86	0	0	000
27	7,000	35	2	62 5	0 5	0	000
28	7,200	35	4	60	1	0	000
July 1	8,800	18 5	0 5	79	0 5	1 5	134*
2	7,000	30 5	0 5	68 5	0 5	0	000
3	9,000	19 5	1	76	1 5	2	180†
5	8,200	2	4	94	0	0	000‡
6	5,000	37	4 5	46 5	1 5	10 5	750§
8	7,400	17	1	82	0	0	000§
9	10,400	19 5	4	69	3 5	4	408§
10	14,800	48 5	2	47	2	0 5	25§
11	16,400	39	3	54	2	2	328§
12							000§
13	20,000	14	1	84	0 5	0 5	100§
15	12,000	60	0	40	0	0	000§
16	17,000	16 5	1 5	79	0	3	510§
17	7,000	54	2 5	42 5	0	1	70§
18	6,800	29 5	1 5	65 5	0 5	3	204§
19	5,400	39 5	0	59	0	1 5	81§
20	4,900	38	4	57	1	0	000§
22	3,800	30	2	68	0	0	000§
23							§
24	7,600	36	6 5	53	4 5	0	000§
25							§
26	8,800	26 5	1 5	68 5	1 5	2	176§
27							§
29	5,400	37	4	58	1	0	000
Sept 23	12,400	12 5	1 5	85	0	1	124
27	10,800	30 5	2 5	66	1	0	00
30	11,000	24 5	2 5	66	4	3	330
Oct 2	15,600	14	1	83	1	1	156
4	10,200	14	4	81	0	1	102
Nov 6	12,000	16	5	78	0	1	120¶
7	7,000	25 5	3 5	62	5	6 5	455
8	8,000	10 5	6 5	81 5	1 5	0	00
9	13,200	31 5	2 5	63 5	2	0 5	66
11	11,200	30	5	61	0	4	448

\*Two c c original extract given intraperitoneally, †3 c c, ‡4 c c, §5 c c

¶Two c c filtrate after coagulation of albumin by heat and acidulation

TABLE 3—BLOOD COUNTS IN GUINLA-PIG 46

Date	No Leuko- cytes	Per Cent Polynu- clears	Per Cent Large Lymph	Per Cent. Small Lymph	Per Cent Baso- phils	Per Cent Eosin- ophils	No of Eosin- ophils
May 8	11,600	37	45	51.5	1.5	2.5	290
20	13,700	39	5.5	53.5	00	2	274*
21	13,400	25	2	69.5	0.5	3	402
22	13,400	12.5	4.5	81	0	2	268†
24	12,400	18	1.5	80	0	0.5	62‡
27	16,000	17	2	79	0	2	320‡
28	13,200						‡
31	9,000	24	11	61	1	3	270‡
June 1	12,200	22.5	5.5	69	1	2	244‡
3	9,000	19.5	2.5	76	0.5	1.5	135‡
6	12,000	35	4.5	55.5	0	5	600‡
7	14,000	25.5	4	66.5	3	1	140‡
8	22,000	15	2	79	2	2	440‡
10	11,000	31	5	60.5	1	2.5	330
11	17,500	13	1	83	0	3	525‡
13							‡
14	19,600	10.5	3.5	80	0.5	5.5	1,078
20	9,000	16	0	84	0	0	00
24	9,800	18	2	77	0	3	294‡
25	12,800	10	2.5	83.5	0	4	512
26	16,000	8.5	3.5	86	0.5	1.5	240
27	14,200	7	2	91	0	0	000
28	12,800	19.5	0.5	78.5	1.5	0	000
29	20,200	11	1	86	0	2	404
July 2	19,400	4	0	95	1	0	000
6	19,800	20	3	71	2	4	732
8	14,200	11.5	0.5	88	0	0	000‡
9	11,000	6.5	1	80	0	3.5	380
10	10,000	29	0	65	1	5	500‡
11	17,200	6.5	0.5	91.5	0	1.5	258‡
12	11,000	5	0	81	0	14	1,540‡
13	11,000	6	2	86	1	5	550
15	10,800	5.5	3.5	87.5	0	3.5	378‡
16	14,000	19	1	71	0	9	1,260‡
17	11,000	18	1	77	2.5	1.5	165‡
18	14,000	13	1	79	2	5	700‡
19	15,000	23.5	1.5	69.5	0.5	5	750‡
20	15,800	16.5	1.5	71	4	7	1,106‡
22	12,800	15	2	72	2	9	1,152‡
23	15,000	16	2.5	72	1.5	7.5	1,125‡
24							‡
25	13,600	9	2	80	2	7	952‡
26							‡
27							‡
29	13,000	11	2	84	1	2	260
Sept 22							‡
23	13,400	13.5	1.5	70	0	15	2,010
25	15,000	24	1	60	2	13	1,950
27	10,800	28	2	54	1	15	1,620
30	7,000	21	4	63.5	0.5	11	770
Oct 2	17,000	16	1	72	0	9	1,460
4	10,200	17	2	76	0	5	510
Nov 6	17,200	24	3.5	66	1.5	5	860‡
7	6,800	29.5	11.5	49	0	20	1,360
8	16,200	23	6	54.5	1	15.5	2,511
9	15,200	22	1	68	4	5	760
11	7,200	18	2	69	2	9	648§
12	10,200	8.5	3.5	86	0.5	1.5	153
13	12,400	12	3	80	0	5	620
14	9,600	8	3	87	0	2	192

\*Five c c original extract intraperitoneally, 72 c c doses

‡Two c c solution in 0.5 per cent saline of protein of extract precipitated by acetone

§Two c c filtrate after coagulation of protein with heat and acidulation

TABLE 4—BLOOD-COUNTS IN GUINEA-PIG 45

Date	No Leuko-cytes	Per Cent Polynu-clears	Per Cent Large Lymph	Per Cent Small Lymph	Per Cent Baso-phils	Per Cent. Eosin-ophils	No of Eosin-ophils
May 8	12,000	31	4	60	3	2	240*
10	9,400	29 5	3 5	61 5	3	2 5	235
15	11,400	32	5	59	2	2	228†
40 min later	10,800	32	0	67	0	1	108
June 5	7,000	19 5	0	78 5	0	2	140‡
10 30 a m							
10 50 a m							
11 30 a m							
4 30 p m	8,000	63	2	27	2	6	480
June 6	16,400	28	1	65	1	5	820
7	9,000	24 5	4 5	56 5	3	11 5	1,035
8	9,600	8	2	86	0	4	384
10	8,600	13	2	85	0	0	00
11	10,800	7	3	85	4	1	108†
12	14,200	12	1	66	6	15	2,030
13	10,000	9 5	3	79 5	1 5	6 5	650
14	9,400	15	2	79	0	4	776
20	17,400	27	1	70	0	2	348
24	11,000	43	1	55	0	1	110†
25	16,400	28 5	2 5	53 5	1	14 5	2,378
26	13,400	20	1	75	0	4	536
27	22,400	32	4	63	0	1	224
28	14,800	36	0	62	2	0	000
29	25,000	11	2	87	0	0	00
July 2	24,400	10	3	86	0	1	224
6	23,600	31	0	65	0	4	944
8	24,200	20	1	76	0	3	726
10	20,000	42	1	56	0	1	200
12	25,200	10	1	88	0	1	252
15	15,000	26	1	73	0	0	00
18	13,000	19	0	81	0	0	00
20	11,600	49	1	44	0	6	696
22	20,600	16	5	78	0	1	206§
23	16,800	14	2	82	0	2	336

\*Weight 320 gm †Two cc extract intraperitoneally ‡Four cc extract intraperitoneally §Weight 650 gm  
Dyspnea, cyanosis, twitching, paralysis

TABLE 5—BLOOD COUNT IN GUINEA-PIG 50 WEIGHT 245 GRAMS

Date	No Leuko-cytes	Per Cent Polynu-clears	Per Cent Large Lymph	Per Cent Small Lymph	Per Cent Baso-phils	Per Cent Eosin-ophils	No of Eosin-ophils
Sept 2							
Sept 23	6,200	38	2	58	1	1	62*
27	4,600	47 5	5 5	47	0	0	00
30	7,600	50	7	39 5	2 5	1	76
Oct 2	6,200	30 5	4 5	61 5	1 5	3	186
4	5,600	36	5 5	56	0	2 5	140
30	5,600	24	1	67	2	6	336†

\*Two ccm extract intraperitoneally

†Two cc solution in 0.5 per cent salt solution of protein of *Ascaris* extract precipitated by acetone Dyspnea, paralysis, death after 45 minutes



TABLE 6—BLOOD COUNT IN GUINIA-PIG 47

Date	No Leuko-cytes	Per Cent Polynu-clears	Per Cent Large Lymph	Per Cent Small Lymph	Per Cent Baso-phils	Per Cent Eosin-ophils	No of Eosin-ophils
June 26	14,600	42	0.5	54.5	0	3	438
27	12,000	32.5	3	62	1.5	1	120
28	8,000	32	2	63	0	3	240
29	11,000	19	1	79	0	1	110
July 5	9,600	34.5	2.5	63	0	0	000*
6	14,000	28	1.5	70	1.5	1	140
8	10,600	18	1	80	0	1	106
10	10,200	25.5	1.5	71.5	0	1.5	153*
11	18,400	55.5	1	40.5	0	3	552
12	25,400	24	2	70	1	3	762
13	14,200	28.5	0.5	67	0	4	562
15	11,600	32	3	64	0	1	116
18	11,800	6.5	1.5	91.5	0.5	0	000*
19	17,800	20	0	71	3	6	1,068
20	15,800	42	0.5	44	2	11.5	1,817
22	11,600	4	2	93	1	0	000
24	12,600	21	1	72	2	4	504*
25	24,400	35.5	0.5	53	4	7	1,708
26	19,600	32.5	2	50.5	2	13	2,548
27	23,600	18	1	75	1	5	1,180
29	8,400	51.5	0.5	40	7.5	0.5	42

\*Two c.c. original extract intraperitoneally

TABLE 7—BLOOD COUNTS IN GUINIA-PIG 36

Date	No Leuko-cytes	Per Cent Polynu-clears	Per Cent Large Lymph	Per Cent Small Lymph	Per Cent Baso-phils	Per Cent Eosin-ophils	No of Eosin-ophils
May 8	16,000	46	4	40	2	8	1,280
20	11,200	44	5	40	1	10	1,120*
21	13,600	46	3	40	1	10	1,360*
22	18,400	20	5	73	0	2	268†
24	16,200	30	1	60	1	8	1,296†
27	7,000	21	4	68	1	6	420†
28	10,600						
31	9,000	39	2	49	2	8	720†
June 1	10,000	31	3	59	2	15	1,500†
3	15,000	19	6	59	1	15	2,250†
4	12,000	19	1	70	1	9	1,080†
5	18,000	28	3	58	1	10	1,800†
6							†
7	7,800	27	1	60	0	12	936†
8	10,400	21	1	69	1.5	7.5	780†
10	13,400	22	0	68	1	9	1,200†
11							†
13							†
14	10,000	10	1	80	0	9	900
20	10,200	24	2	56	0	18	1,836
24	15,000	19	5	63	2	11	2,650
25	14,400	37	3	49	2	9	1,296
July 2	26,000	15	2	79	2	2	520
5	27,800	18	1	75	0	6	1,668

TABLE 7—Continued

Date	No Leuko- cytes	Per Cent Polynu- cleus	Per Cent Large Lymph	Per Cent Small Lymph	Per Cent Baso- phils	Per Cent Eosin- ophils	No of Eosin- ophils
8	23,700	21	0	74	0	5	1,185
10	24,200	24	2	65	0	9	2,178
12	27,800	27	0	60	0	13	3,618
15	25,000	37	1	56	1	5	1 250†
16	31,600	46	0	43	1	10	3,160
17	22 800	28	1	65	0	6	1,368
18	32,800	23	1	69	1	6	1,968
20	28,600	24	0	62	1	13	3,618
22	23,600	33	0	44	1	22	5,172
23	22,000	27	0	63	1	9	1 980
26	21,600	38	0	53	0	9	1,944
29	13,000	40 5	2 5	38	3	16	2,080
Sept 23	15,000	28	3	54	0	15	2 250
27	9,800	32	3 5	45 5	1 5	17 5	1,715
Oct 2	12,000	22	3	56	0	19	2 280
4	10,000	14	1	71 5	2 5	11	1,100
Nov 6	13,800	30	3	43	2	22	3,036‡
7	11,000	22 5	0	54	2	21 5	2,365
8	12,800	27	4	44	2	23	2,944
9	15,600	15	5	60	2	18	2,808

Five c c original extract intraperitoneally, <sup>†</sup>2 c c <sup>‡</sup>2 c c extract previously boiled

TABLE 8—BLOOD COUNTS IN GUINLA-FIG 48

Date	No Leuko- cytes	Per Cent Polynu- cleus	Per Cent Large Lymph	Per Cent Small Lymph	Per Cent Baso- phils	Per Cent Eosin- ophils	No of Eosin- ophils
Sept	23	8 400	42	1	55 5	1 5	00
	27	13,200	46 5	4	48 5	0	132
	30	10,000	25	2	72 5	0 5	00 <sup>†</sup>
Oct	1	13,000	66	2 5	28	0	3 5
	2	11,600	60 5	3 5	32	2	232
	4	8 800	19	0	80	1	00
	7	12,000	21 5	2	76	0	0 5
	9	14 400					
	30	8,500	37	4	57	1	1
	31	8 000	19 5	8	64 5	4 5	3 5
Nov	1	10 800	40	2	46 5	0 5	11
	2	5 400	16	2	78	0	4
	6	10 000	41 5	2 5	53	1	2
	7	16 400	40 5	4	34 5	3	18
	8	11 200	30	2	67	0	1
	9	13,400	25	10	59 5	1	4 5
	11	11 000	27 5	7 5	61 5	0 5	3
	12	11 000	32	4 5	63	0	0 5
	13	7 200	13	4	83	0	00
	14	8 600	21	1	75	2	1

\*Two c c extract intraperitoneally

<sup>†</sup>Two c c extract intraperitoneally (solution previously boiled)

<sup>‡</sup>One and five tenths c c solution of acetone precipitate injected intraperitoneally

<sup>§</sup>Two c c filtrate after coagulation of albumin of extract by heat and acidulation

## THE ARCHIVES OF INTERNAL MEDICINE

TABLE 9—BLOOD COUNTS IN GUINIA FIG. 53

Date	No Leuko- cytes	Per Cent Polynu- clears	Per Cent Large Lymph	Per Cent Small Lymph	Per Cent Baso- phils	Per Cent Eosin- ophils	No of Eosin- ophils
Dec 6	18 200	36	2	54	0	5	1,456*
7	21,000	72 5	6 5	11	1	6	1 260
11	22 800	36	7	45 5	3 5	5	1 824
13	20 000	50	11 5	35 5	0 5	2 5	500
16	10 200	27	7	60	0	6	612†
17	30 000	66	11	14	1	8	2,400*
18	11,800	43	1	40	1	12	1,416*
19	4 800	34 5	6 5	76 5	0 5	2	96*
20	9 400	30	1	57	2	7	658

\*Two cc extract intraperitoneally, 1 cc extract intraperitoneally, dyspnea, tremor, convulsive movements

TABLE 10—BLOOD COUNTS IN GUINIA FIG. 34

Date	No Leuko- cytes	Per Cent Polynu- clears	Per Cent Large Lymph	Per Cent Small Lymph	Per Cent Baso- phils	Per Cent Eosin- ophils	No of Eosin- ophils
May 8							150*
19, 15	10 000	23 5	3	70 5	1 5	1 5	408†
June 3	10 200	8	0	88	0	4	270
3 p m	9 000	13	1 5	82 5	0	3	700
4 30 p m	11 000	14	1	48	1	5	
June 4							1,384
2 p m	19,600	44	1	44 5	3 5	7	1 400
4 p m	14,000	39	3	46	1	10	850
June 5	17 000	15 5	2	78	0 5	5	1,840
6	8 000	17	0	60	0	23	1 140
7	12,000	4 5	4	82	0	9 5	488
8	12,200	19	0 5	76 5	0	4	428*
10	17 600	38	2	57	0 5	3	1,680
11	21,000	37 5	2 5	51 5	0	8	3 168
12	19 800	27	4	53	0	16	576
13	14,400	7 5	1	86 5	1	4	1 200
14	12,000	20	2	65	0	10	320
20	16,000	20	0 5	77 5	0	2	504*
24	16,800	24	1	68	0 5	3	2,800
25	28,000	23	1 5	67	2	10 5	2,613
26	13 400	33 5	0	45	1	3	360
27	12,000	4	1	91	1	3	378
28	12,600	4	3	89 5	0 5	6	744
29	12,400	25	1	67	0	4	480
July 2	12,000	2 5	0	92 5	1	9 5	1,615
3	17,000	37	1 5	50	1	1	130
5	13 000	24	1	74	0	5	420
8	8,400	24 5	1	68 5	1	5	710
10	14 200	29	2	62	2	1	96
12	9,600	2	1	96	1	7 5	675*
15	9,000	33	0	59 5	0	4	728
16	18 200	18	0 5	76 5	1	21	3,192
17	15,200	33	1	45	0	8	1,568
18	19 600	20	2 5	69 5	0	6	924
20	15 400	35	2	57	1 5	5	650
24	13 000	1 5	1	71	1	7	1,190†
27	17 000	23	3	68	1	15	2,040
29	13,600	32		49			

\*Two cc extract intraperitoneally

†Two cc extract intraperitoneally 2 p m

# UNSATURATED FATTY ACID AS A NEUROLYTIC AGENT<sup>\*</sup>

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This communication is a brief report of some experiments conducted with the purpose of determining whether certain hemolytic substances had a lytic effect on the nerve cell and what the consequences of this lytic action might be in the surrounding tissue. Experiments were conducted on five cats. The substances employed were oleic acid and triolein. Oleic acid, as is well known, is hemolytic, whereas triolein is not. Oleic acid is an unsaturated fatty acid, and on that account, as Faust and Tallquist<sup>1</sup> have shown, is hemolytic. It is capable of forming soaps with bases, and therefore of going into colloidal solution in the body fluids. Triolein is a combination of three molecules of oleic acid attached to a molecule of glycerin. It is a neutral fat, that is, it is not capable of forming soaps with bases and therefore can not go into colloidal solution in the body fluids. Triolein may, under suitable conditions, be emulsified in watery solutions. The difference in hemolytic action is, therefore, dependent on physical causes. The triolein, which contains three molecules of unsaturated fatty acid, does not hemolyze the red cell because it can not reach it, being present as an oil, however finely divided, and therefore unable, probably, to pass through the wall of the red cell. Oleic acid being able to go into colloidal solution is able to pass through the wall of the red blood-cell and mix colloiddally with the contents.

In two cats oleic acid was injected into the brain, in three, triolein was injected under similar conditions into the brain.

## PROTOCOLS

The protocols in brief are as follows:

*Cat 98*—Jan 31, 1912. The cat was etherized at 9:50 a. m., shaved, and the operation started at 10:30. An incision was made a little to the right of the median line about 1.5 cm. in length. The skull was trephined in about the center of this incision and 0.1 cc. of oleic acid was injected. The wound was closed with two black silk sutures dried with ether, and covered with collodion and cotton.

Feb. 3, 1912. The cat seemed to have recovered from the effects of the operation and was put in with the other cats.

Feb. 6, 1912. The sutures were removed and an attempt was made to reenter the brain with a needle. In doing this the wound was opened. 0.3 cc. of oleic acid was injected in all 0.1 cc. in each of three places. The last injection went the deepest downward and backward. The etherization was begun at 3:05 p. m.

<sup>\*</sup> Submitted for publication in *THE ARCHIVES* Dec. 6, 1912.

<sup>\*</sup> From the Laboratory of the Danvers State Hospital. No. 24 of the Danvers State Hospital Series.

<sup>1</sup> Faust and Tallquist. *Arch. f. exper. Path. u. Pharm.* 1907, lxx, 375.

and the operation completed at 1:15 p. m. The wound was again closed with one silk suture, dried and covered with collodion and cotton. The cat was found dead the next morning. The skull was opened and the brain removed. There was a hemorrhage at the site of the injection.

*Autopsy*—The findings at autopsy were as follows. The gross section of the brain showed a large hemorrhagic focus in the white substance. The individual injections could be made out. The lesion had a chocolate brown color which is characteristic of the combination of oleic acid and blood. It is noteworthy that the discoloration was not confined entirely to the site of the hemorrhage, but extended throughout the white matter in the neighborhood so that on the affected side the gray matter appeared pale by contrast the reverse of normal as shown

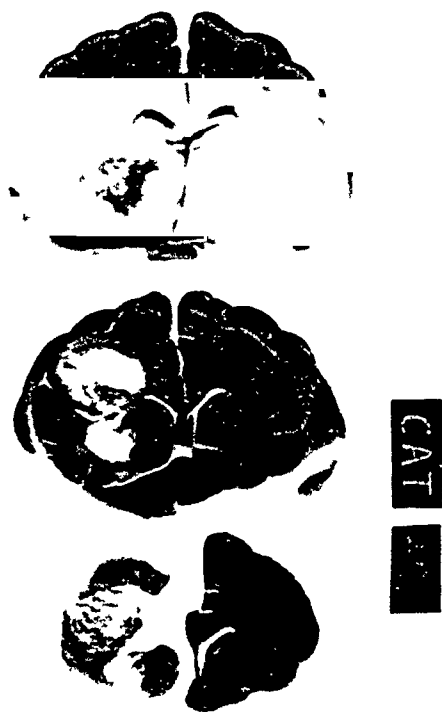


Fig. 1—Brain of Cat 98. Four injections of 0.1 cc oleic acid each in about the same place into right hemisphere. Extensive hemorrhage. The right hemisphere is pushed over towards the left in the region of the median fissure. Convulsions show no flattening.

on the left side. The anterior portion of the hemorrhage represented the older of the injections (about a week between the injections). There were no signs of intracranial pressure at autopsy, yet the right hemisphere was distinctly enlarged by the injection, as might be seen in the cross section by the bulging of the median fissure.

*Microscopical Examination*—Microscopically the hemorrhage itself showed a marked destruction of red blood cells. The resulting brown pigment and detritus that filled the area of the lesion could account for the macroscopic dark color. In the neighborhood of the lesion this pigment and detritus was scattered thinly



Fig 2 —Brain of Cat 104 Two injections of 0.1 cc oleic acid at two different points within the right hemisphere Distinct focal hemorrhages Apparently no great displacement of tissue

between the cells. The nerve cells had not taken up any. Here and there the nerve cells, however, were filled with globules of varying size that stained intensely with Scharlach R. There was here and there about the periphery of the lesion an amorphous hyaline substance staining a pale blue with hematoxylin and thionin probably a calcium soap. There was a marked destruction of nerve cells and neuroglia the nerve cells showing various stages of degeneration (vacuolization etc.). Some nerve cells showed distinct satellitosis. There was a marked increase of perivascular cells. The endothelial cells about the vessels appeared to be filled with the brown pigment and granules taking the Scharlach R rather indistinctly. The neuroglia at the membrana limitans of the brain tissue had become more active. The connective tissue cells around the blood vessels had large vesicular nuclei and might possibly be active. All along the course of the blood vessels were cells with involuted nuclei that might be lymphocytes. The vessels were filled with fat. The increase of cells about the vessels was comparable to the increase of neuroglia cells.

*Cat 104*—Feb 27, 1912. Etherization was begun at 9:10 a. m. and completed at 9:30 a. m. An incision about 1.5 cm. was made just to the right of the median line and the skull was trephined. One tenth cc. of oleic acid was injected in each of two places. The wound was closed with silk sutures and covered with collodion and cotton. The operation was completed at 10:10 a. m. The cat did not recover fully from the ether and died in the early part of the afternoon. On removing the calvarium the dura was found to be torn apparently by the trephine. There was a hemorrhage over the point of injection extending over the side of the brain to the inferior surface. There was a brownish deposit of oil in the dura under the brain.

*Microscopical Examination*—The duration of this experiment was only a few hours. The destruction of the blood cells at the site of the main lesion was not as complete as in the previous experiment but was nevertheless very marked. In the neighborhood of the lesion there was a large amount of detritus and blood-pigment in the brain substance. The reaction around the vessels observed in the foregoing experiment was not noticeable here although here and there there was an indication of a beginning proliferation. In the immediate neighborhood of the lesion some of the nerve cells showed destruction. There was a marked satellitosis about these cells which was not noticeable at a distance from the lesion.

*Cat 103*—Feb 27, 1912. Etherization was begun at 10:05 a. m. and completed at 10:40 a. m. The incision was made just to the right of the median line and the skull was trephined. There was considerable hemorrhage of apparently venous blood. This was finally checked and 0.2 cc. of triolein was injected in one place. The wound was closed with two black silk sutures dried, and covered with collodion and cotton. The operation was completed at 11:25 a. m. Later in the afternoon the cat was rather stupid and in a semiconscious condition.

Feb 28, 1912. The cat was found dead in the morning. The skull was opened and the brain removed. There was a hemorrhage beneath the dura at the point of injection. There was also a hemorrhage in the right lateral ventricle.

*Cat 105*—Feb 29, 1912. Etherized at 9:10 a. m. Operation begun at 9:55 a. m. The skull was trephined in about the same place as in the other cases and 0.1 cc. of triolein was injected. The wound was closed with silk suture dried and covered with collodion and cotton. The operation was completed at 10:10 a. m. The cat recovered from the ether very easily and seemed perfectly normal.

March 1, 1912. The cat was well and quite playful.

March 2, 1912. The cat was chloroformed and the skull opened and the brain removed. There was a slight hemorrhage beneath the dura at the point of injection.

*Cat 106*—Feb 29, 1912. The cat was etherized at 10:20 a. m. The operation was begun at 10:35 a. m. The skull was trephined on the right side and there was considerable bone hemorrhage. This was finally checked and 0.3 cc. of triolein

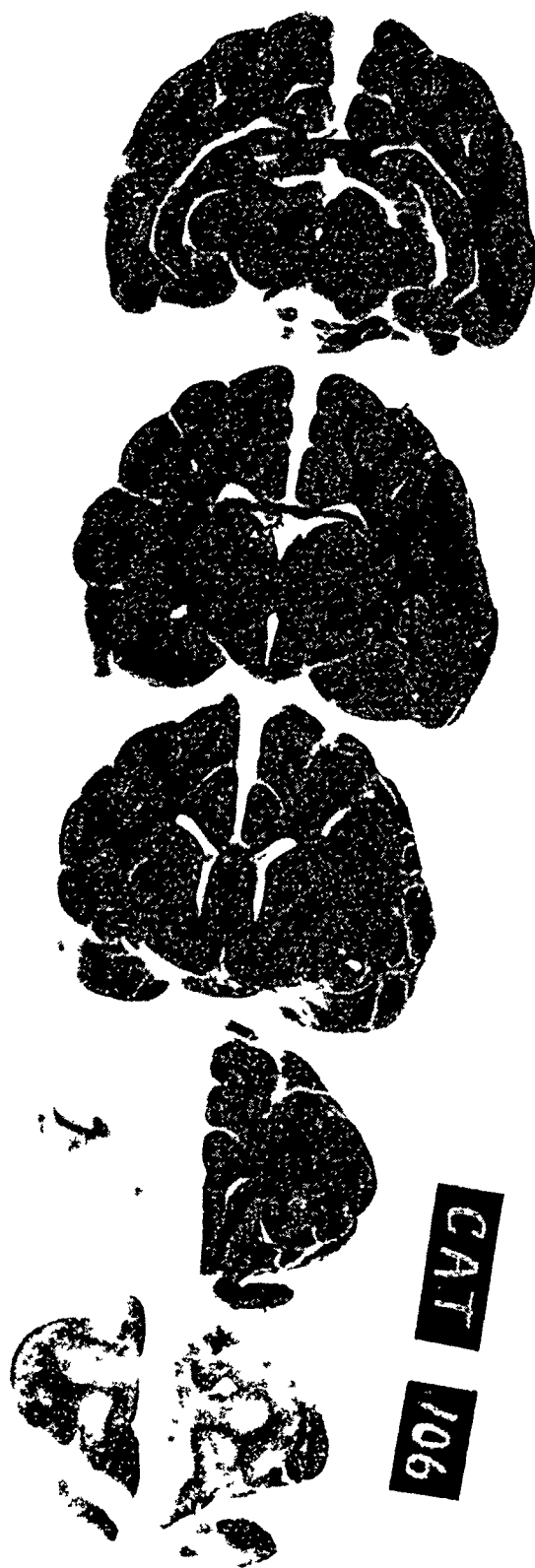


Fig 3—Brain of Cat 106 This picture shows the appearance of the brains of the three cats injected with triolein instead of oleic acid 0.3 cc of triolein was injected into one place in the right hemisphere Two days later the brain was removed No hemorrhage No sign of the injected oil except microscopically



was injected in one place in the right hemisphere. The wound was closed with three silk sutures, dried and covered with collodion and cotton. The cat recovered from the effects of the ether and seemed normal.

March 1, 1912. The cat was well and willing to be petted and to play with a straw.

March 2, 1912. The cat was chloroformed, the skull opened, and the brain removed. There was little to see externally except a slight congestion at the point of injection.

*Microscopical Examination of the Brains of Cats 103, 105, 106.*—With the exception of Cat 103 there were no signs of hemorrhage in these three cats. In 103 the hemorrhage was probably caused by a dull trephine rather than by the injection, as venous blood poured out from under the dura during the operation. The hemorrhage was confined to the subdural space and the lateral ventricle. The reactions, such as perivascular proliferation, nerve cell alteration, satellitosis and the appearance of the brown detritus due to the destruction of the blood cells were either mild or in the latter case absent. (Cat 103) which had a hemorrhage showed microscopically practically no hemolysis. At the site of the hemorrhage there was a large amount of unabsorbed fat, apparently unaltered triolein. There was considerable unaltered triolein in the meshes of the pia mater. The pia cells appeared quite active. (Cat 105 showed microscopically a small hemorrhage into the white substance. This hemorrhage in Cat 105 as in Cat 103 is to be regarded as mechanical in origin as evidenced by its small size and by the absence of hemolysis and blood pigment and detritus in its vicinity. The endothelial cells about these hemorrhages had taken up what fat they could but there seemed to be no evidence of increase in the number of endothelial cells.

The reaction therefore seems in the case of triolein injections to be confined to the site of the injection and to the immediate disposal of as much triolein as possible, whereas in the case of oleic acid the size of the intracerebral hemorrhage, the nerve cell alteration, such as vacuolization, satellitosis, perivascular reaction and the appearance of the brown granular pigment indicate a more or less destructive action on the nerve cells as well as on the red blood-cells. The perivascular proliferation and the satellitosis might, in view of these experiments, be regarded as of a protective nature, having possibly to do either with the neutralization of the unsaturated fatty acid or with the handling of the products of the destruction of the nerve cells (satellitosis).

#### SUMMARY

1. The above experiments show that unsaturated fatty acid, of which oleic acid is the type, is a neurolytic agent.

2. It is probable that this neurolytic action depends on the same properties as the hemolytic action of these substances.

3. Perivascular proliferation and satellitosis may be associated with pathological processes in which lytic fatty substances play an important part.

4. An intracerebral hemorrhage may be produced experimentally without altering the blood-pressure and without trauma, but by means of chemical action alone.

5. A method is hereby given for producing hemorrhages within the nervous system at any desired point.

# A CRITICAL STUDY OF A CASE OF MYIASIS DUE TO *ERISTALIS* :

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Sept 2, 1912, one of us (Muir) was called in to see a boy, J. H , 5 years old, who had been ailing for about ten weeks and who was under medical treatment for indigestion and obstinate constipation for about five weeks of that time The child was emaciated and anemic Very striking symptoms were the constant and pronounced twitching of the eyelids and other nervous movements He gritted his teeth in his sleep at times, and made convulsive movements of the limbs When awake he complained of pain in the limbs and of headache The emaciation seemed to be due to the fact that the boy had for some time vomited almost everything he ate The breath was very bad, "worse than rotten eggs," according to his parents

On the basis of the nervous and digestive disturbance and the general debility, a diagnosis of worm infestation was made The mother was told to call and get some medicine, but instead of doing so she bought a bottle of a proprietary worm remedy, on the advice of a neighbor, and gave the child a dose, according to the directions, at noon of September 3 The stool was passed at evening into the slop jar which was in regular use The jar had been rinsed with city water from the hydrant in the morning and allowed to dry during the day There is no water on the place except that of the Colorado Springs water system, available at a hydrant in the yard and a sink tap in the house On looking at the stool immediately after its passage, the boy noticed a strange object moving around in it and called the father and mother to see it They found the object wiggling around vigorously in the feces and urine, and attempting at times to climb up the sides of the jar The specimen was removed and put in water, in which it thrashed around for a time, and was then put in alcohol, in which it shriveled considerably, according to the mother and father The specimen was turned over to Muir, who referred it to Dr Trossbach of Colorado Springs It was sent by him to Mr W W Cort of Colorado College, who referred it to Hall, then in Colorado Springs on government field work, for identification

The specimen is one of the "rat-tailed larvae," a larva of one of the family *Syrphidae* of the order *Diptera* or flies The mother states that

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\*From the U S Bureau of Animal Industry, Washington, D C

the larva was originally yellowish with three brown stripes, but when it came into our hands it was black over the entire body except for a little brownish coloring on the "tail." The anterior part, or body proper, is 1.55 cm. long, while the "tail" is 1.65 cm. long, a total length of 3.2 cm. This "tail" is really the breathing tube of the animal. These larvae live in soft mud, wet manure, privies and other places where there is plenty of sufficiently moist food, and the "tail" is a stigmatic tube which is held projected upward at the angle necessary to keep the tip above the wet material in which the larva lives, thereby enabling it to bring down a supply of air for breathing.

Williston (1886) in his synopsis of the North American *Syrphidae*, describes the larvae as follows:

The larvae are usually not very elongate, with firm, sometimes tough skin, the head segments small and extensible. Like the other families of the *Cyclorhapha*, the larvae of *Syrphidae* do not have a distinctly differentiated head. The external mouth parts are either wholly wanting with only a soft fleshy opening, or there are two or four outwardly directed hooklets. There are also short small, one or two jointed fleshy antennae. The body is smooth or provided with soft, conical projections and bristles, below usually with seven pairs of abdominal feet. At the posterior end, the body terminates in a more or less elongate tube, single or double—the stigmata. This sometimes forms a short, almost chitinated, tubercular projection on the dorsal part of the last segment, at other times it is very long, longer than the body, slender, composed of two joints, the one sliding within the other, like the joints of a telescope. It is never divaricate, or forked at the tip, as in many of the other tailed larvae in the allied families.

Supposed cases of gastric or intestinal myiasis should always be given very careful consideration and investigation. Our actual knowledge of the subject is limited. To what extent various dipterous larvae, commonly occurring as free-living forms, can survive the digestive processes of the alimentary canal and pass out in the feces undigested and even alive and uninjured, is something of which we have too little information. How long such larvae could persist in the alimentary canal, deriving their nourishment from the digested food of the host, and then air supply from the ingested atmospheric air, can not yet be said. We may surmise, and plenty of surmising has been done, but the fine field for experimental investigation which the subject affords is untouched except for such few records as those of Alessandrini (1909), who has fed the cheese skipper, *Prophila casei*, to dogs and finds that it passes through the digestive tract alive and uninjured, causing intestinal lesions in the dog. Even the information which would be furnished by the publication of carefully investigated cases is to a large extent, lacking. Banks (1912) quotes Walsh as follows:

Taking everything into consideration, we doubt whether, out of ten thousand cases where the larvae of two winged flies have existed in considerable numbers in the human intestines, more than one single case has been recorded in print for the edification of the world by competent entomological authority.

In addition to our lack of adequate knowledge of the possibility of facultative parasitism on the part of various fly larvae, there is the certainty of error in some cases, due to deliberate fraud on the part of hysterical patients or to accidental contamination of the stool. So many things are sent to specialists for identification as parasites, which prove to be free-living forms incapable of parasitic modes of life, that anything other than an obligate parasite demands a careful investigation. When a farmer states that he defecated in or near the stable and found worms in the stool, and the worms prove to be "rat-tailed larvae," it is much more likely that the larvae were already in the manure at the place of defecation than that they were actually passed. And even when such larvae are found in the slop jar where the jar has been rinsed with water from an open spring, the possibility of the larvae having been in the spring and having remained in the jar after rinsing must bring the find under suspicion.

Dr Albert Hassall of the Bureau of Animal Industry has related to one of us (Hall) an instance which indicates the need of care in passing on cases of myiasis. He states that on one occasion he saw a slop jar, kept in a privy during the day and only brought in for use at night, with a larva of *Ernstalis* hanging over it, just ready to drop, while it was in the privy. Had the larva fallen unobserved and been found at the appropriate time, it would have been ample evidence to most persons that it had been passed into the jar by the persons using it.

Of myiasis in general, Banks (1912) says

There is a considerable number of flies whose larvae either regularly or occasionally live in substances used by man as food. The great majority pass through the intestinal tract without our knowledge, for most of them cause little or no trouble. But sometimes with patients in hospitals or asylums, or in private practice, the physician discovers these maggots, and often suspects them of causing the malady or weakness of his patient.

Many such specimens have been sent to entomologists, but owing to the fact that no one had studied these forms, their characters were little understood, and the identifications have not been of much value. Most of these larvae belong to a few closely related families of flies that were formerly covered by the name *Muscidae*. The arrangement of the flies has been the subject of much diverse opinion, while the knowledge of the larvae is very fragmentary.

When we consider that these dipterous larvae occur in decaying fruits and vegetables and on fresh and cooked meats, that the blow-fly, for example, will deposit on meats in a pantry, that other maggots occur in cheese, oleomargarin, etc., and that pies and puddings in restaurants are accessible and suitable to them, it can readily be seen that a great number of these maggots must be swallowed by persons each year, and mostly without any serious consequences. Besides these there are the fruit flies, whose larvae live in apples, cherries, gooseberries and oranges, and the pomace flies that hover around grapes, pears, and other fruits.

So far as we have been able to locate it, the literature relating to the subject of myiasis due to larvae of the *Syrphidae*, is as follows:

Odhelius (1789) records a case from Carlstad, Sweden, in which fly larvae, determined as those of *Musca pendula*, were claimed by Dr

Flanck of that place to have been passed by a 17-year-old girl patient. The patient had been in good health until three years previous, and then became sickly, complaining of severe pain in the stomach, of giddiness and headache, inflammation of the throat, and such great weakness that she was often compelled to go to bed. In the summer of 1787 she had to have medical treatment. At that time mineral waters were prescribed, jalap, aloes and calomel were administered, and as a result these larvae were dislodged and the patient returned to her former health after some weeks. The patient's diet previous to the time she became sick consisted largely of milk, and included occasionally sour curdled milk from the country. She was very fond of cheese rind or the outer part of cheese. Odhelius suspects that the patient became infested by ingesting eggs laid by the fly either in the cream on the sour milk or on the surface of the cheese.

Joseph (1887) notes this case and parenthetically notes that the larvae were probably *Homolomyia canicularis*, but since Odhelius specifies them as rat-tailed larvae there seems to be little warrant for Joseph's assumption. It seems probable that this is the case referred to by Gilbert (1908) as a record of *Eristalis pendulus*, by Brumpt (1910) as one of *Helophilus pendulinus*, and by Gedoelst (1911) as one of *Tubifera pendula*. It appears from Coquillett (1910) that the correct name is *Helophilus pendulus*, the type species of *Helophilus* being *Musca pendula*. According to the same authority, *Eristalis*, type *Musca tenax*, is merely a synonym of *Tubifera*, but in a paper of this sort we have thought it better to adhere to the commoner and more generally used name.

Wagner (1870) records a case of infestation with *E. arbustorum*. One of four to six specimens was sent to him by Dr. Kind and the adult fly was bred and determined by him. The larvae were passed, following a dose of rhubarb, by a woman who imagined she had worms. Dr. Kind had carefully examined the feces of the patient every day since the beginning of March, the larvae being passed on March 10, and had also made such careful examination of the other circumstances in the case as to leave no doubt as to the origin of the larvae. The circumstance which makes the finding especially plausible is that only an occasional pupa, and never a larva, survives the winter. The previous winter had been very severe and he surmises that it would require some explaining to clear up the question as to where this larva had come from at the beginning of March if this was not a good case of myiasis. Wagner points out that the conditions in the digestive tract simulate closely the ones in which the larva lives in Nature, that there is plenty of air, warmth and food, and even such mephitic gases as those with which the larva is usually surrounded. He is of the opinion that probably the larvae were located

in the stomach after the habit of *Gastrophilus*, rather than in the intestine. He notes that he has not infrequently found rain water draining from compost heaps into inadequately protected springs, and considers it very probable that *Eristalis* eggs from compost heaps and the like would be ingested in drinking water.

Brumpt (1910) has erroneously referred this case to Joseph (1887). Joseph merely quotes Wagner's case.

Leidy (1874) has the following note.

Prof Leidy \* \* \* remarked that Dr Keyser, of this city [Philadelphia], the evening previously had brought to him for examination a worm, which was stated to have been removed from the cavity of the nose of a patient. He recognized the worm as a rat-tailed larva apparently of the genus *Eristalis*, and inquired of those members interested in entomology, if they had ever known this insect to be found as a parasite in the human body. Both Drs Le Conte and Horn said that they had never heard of this genus being parasitic.

Riley (1890) notes "the sending of *Eristalis dimidiatus* in the larva state by Dr J. W. Compton, of Evansville, Ind., who stated that they were passed from the bowels of a young woman," and "the recent sending of larvae of *Eristalis tenax* by Dr J. A. Lintner, to whom they had been sent as having been found under similar circumstances."

Riley and Howard (1890) quote the following from a letter from Dr. Frontis, of Johnston, S. C.

I send by mail to-day a specimen of a small worm that infests a well at this place. Ordinary cleaning of the well does not get rid of them, but they are quickly redeveloped, so that one bucket of water will frequently contain three or four. As a matter of course the water is not used for drinking purposes, but the proprietor would like to use it and be freed from these pests.

A similar case is noted in the files of the U. S. Bureau of Entomology of specimens received from Lime Rock, R. I., in December, 1894, with a report that there were millions, apparently all dead, in a well.

The "worms" in both cases were determined as *Eristalis*, probably *E. tenax*. This, of course, indicates at once one source of human infestation.

Shattock (1908) has an observation on the larvae of *Eristalis tenax*, three specimens of which were sent in from Totten, Hants (England), with the statement that twenty or thirty had been passed at one time and some others singly after a few days' interval. "Full doses of santonin, and of mercury, and other intestinal antiseptics had been given." The collector, Mr. H. McQuade, writes "There is not the smallest doubt but the specimens were passed by the bowel, the whole length of time they were observed was about four weeks, and none have been seen since those which I sent were passed." The patient had recently arrived from France, where she had eaten a good deal of water-cress. In comment, Shattock says:

In the present case the ova were most probably taken by the patient concealed in watercress and subsequently underwent development into larvae in the intestinal canal. When it is remembered that sewers constitute one of the habitats of the larvae there is nothing surprising in the presence of the latter in the contents of the intestine. The oxygen for respiration during their development would be furnished, one must believe, by the air naturally swallowed.

McC Campbell and Coiper (1909) report a mixed infection with *Musca domestica*, *Anthomyia canicularis* and *Eristalis tenax*, and say of the last-named "Cases of myiasis with *Eristalis tenax* larvae are extremely rare. No cases are recorded in which accurate data are given. It is the rarest of the three species considered in this report." Their critical study of their case is not convincing and such hypothetical explanations of the abundance of larvae as due to the reproduction of the larvae within the intestine, or the development of the adult fly and subsequent oviposition in the intestine, are quite at variance with known facts. They state that cathartics and aperients have failed to eliminate the larvae. In this connection it may be noted that in our case an anthelmintic seems to have been satisfactory.

From the general statements of Brumpt (1910) and Geddoelst (1911) one would infer that the larvae of *Eristalis dimidiatus* and of *Helophilus pendulus* have been observed in several cases but we are unable to locate any published records other than those given here.

Gilbert (1908) says of the *Symphidae*

But few cases are recorded of infection by larvae of this family and these all by larvae of the genus *Eristalis*, which are found in decaying vegetables and fruits, and in decaying organic matter of all kinds, or in water saturated with organic remains. The following species are reported to have been passed from the bowels, but no definite history of the manner of infection or of the duration of their parasitic existence is given: *Eristalis dimidiatus*, *Eristalis tenax*, *Eristalis arbustorum*, *Eristalis pendulus*.

Banks (1912) says

There are other flies whose larvae are sometimes reported as swallowed by persons, particularly the rat-tailed larvae of *Eristalis*, which sometimes gets into drinking water.

In the Bureau of Animal Industry collection of parasites there is a specimen of *Eristalis* larva collected in Portland, Me., in 1899, and said to have been passed by man. There is no further information in regard to the case. There are also eight *Eristalis* larvae sent in from Laurel, Md., in 1909, with the statement that they were passed in a jelly-like substance from the vagina of cattle. In correspondence relative to these specimens, Dr. B. H. Ransom suggests to the sender

Probably a diseased condition of the organ in which you found these larvae created an odor which attracted the flies to this particular place with the result that they have deposited their young in the unusual location.

Through the courtesy of Dr L O Howard and Mr R S Clifton, of the U S Bureau of Entomology, we note the following records from the files of the bureau

A larval specimen of *Eristalis* sp was received from a physician in Adell, Wis, in September, 1910, with the report that it was passed by a patient

A similar specimen was sent in from Syracuse, N Y, in October, 1906, with a statement that it was supposed to have been vomited by a woman suffering from vomiting of pregnancy

A larva of *Eristalis* sp or *Helophilus* sp was sent in from Bessemer, Ala, in October, 1905, with a statement that twenty-four of them had been passed by a colored child 19 months old after severe intestinal irritation

Another larva of *Eristalis* sp or *Helophilus* sp was sent in from Pittsburgh in October, 1905, with the report that it was taken alive from the stool of a man who had just returned from a hunting trip and who had drunk stagnant water on the trip

It appears to be customary to refer most cases of rat-tailed larvae to *Eristalis tenax* An examination of the available entomological literature does not furnish us with an adequate description of the larvae of the various species of *Eristalis*, and in fact indicates that these, like many other of the *Diptera* larvae, are not well known The very useful paper on diptera larvae by Banks (1912) unfortunately does not deal with the *Symphidae* The fact that *E tenax* is very common and widely distributed is possibly the warrant for many of these identifications. For ourselves we are unable to identify our specimen closer than to say that it is a larva of *Eristalis*, and possibly of *E tenax* for the reason given—that this is a common species

The mother of the boy from whom our specimen was obtained states that a second larva was passed the morning after the first, but that it was dead, and as it was injured in getting it from the feces it was thrown away Two days later a third specimen was passed and was kept This was later turned over to us and proved to be a curd of some sort, a spurious parasite superficially resembling the first It is possible that the second specimen, which was thrown away, was something similar

Since the passage of the first larva the child has improved in health considerably and his appearance is now that of the normal healthy child The nervous symptoms have disappeared and the persistent vomiting has ceased Food is retained and digested, and the breath is no longer unpleasant

The boy has lived in Colorado Springs for four years, so that the infestation, if genuine, must be referred to this place He had been ailing for several weeks, becoming worse July 28, 1912 The previous evening he had eaten some peaches which his mother says were over-ripe The day following the eating of the peaches the boy did not feel well and asked to be taken for a car ride to Stratton Park, an outlying city park On the way out he vomited repeatedly, and as the vomiting continued



after they arrived at the park, they returned home. From that time the vomiting persisted, accompanied by an obstinate constipation and loss of weight, until the passage of the larva.

Not far from the house, perhaps 150 yards away, is an irrigation ditch which has running water in it part of the time and standing pools of water when the headgate is shut. Quite a little trash and refuse, including kitchen refuse, rotten vegetables, and even dead animals, are dumped in this ditch by careless persons. The boy and his companions play in this ditch and the boy says he has drunk of the water in the ditch. He also plays around a neighbor's stable and during the very rainy July of this year the stable manure would have afforded an excellent place for the breeding of rat-tailed larvae.

There are, then, three apparent chances for infection—the stable, the ditch and the over-ripe peaches. The onset of the vomiting following the eating of the peaches points to them as a possible source. "Overripe" is, of course, merely another word for decaying, and these larvae live in decaying vegetable matter among other things. The fact that the boy had been ailing before eating the peaches, suggests that the infestation antedates the eating of the peaches. The ditch is another likely source of infestation, as a larva breeding in the soft mud of the pools may have been ingested by the boy in water from the pools or in the muddy ditch water as the larva was swept along by the current. There is no obvious way in which the boy would get the larva from the stable except by eating it. While we do not think this likely, it is a possibility that must be kept in mind. Cases of children who have deliberately eaten insects and their larvae are by no means unknown.

As intimated earlier in this paper, there are three possibilities as to the truth or falsity of this case as one of myiasis. Either there was deliberate fraud on the part of the child or its parents, or the stool was contaminated, or the case is a genuine example of gastric or intestinal myiasis.

All the evidence is against the idea of fraud. The parents appear to be rational, sensible and respectable people. They are hard-working persons with no evidence of hysterical tendencies or nervous disorders. They had looked on the specimen as an intestinal worm and were inclined to be incredulous when told that it was a larva or maggot; they had never seen maggots with "tails" before and volunteered that they would look for them after this. They further exhibited an astonishment that was not simulated when told that other cases of the sort had been reported, so they were not imitating other cases. No attempt was made to advertise the find or to excite surprise or sympathy with it. They had looked on it as a banal case of "worms." We consider it out of the question that either of them should have deliberately put the larva in

the slop jar The preservation of the third specimen, a spurious parasite, argues against the idea At the time the boy defecated, the entire family was undressed ready for bed, a thing which eliminates the idea of the boy's deliberately contributing the specimen at that time There is no reason to suspect the boy of such a thing, and no likelihood that a 5-year-old child could successfully, or would, carry around a large, violently wriggling larva for the purpose of fooling anyone in this way It is extremely unlikely that he would do so during the afternoon and out of the question that he could do so when undressed and ready for bed

The possibility of contamination of the stool, so far as we can see, is entirely a question of whether the larva was bred in or washed into the Colorado Springs water system, passed its screens, survived the pressure, entered the slop jar when it was washed and rinsed out in the morning, remained there all day, alive and unnoticed, after the jar dried, as it very quickly would in the dry air of Colorado Springs—the actual atmospheric humidity being low even on rainy days—and was then found after defecation This seems very unlikely and even, in our opinion, out of the question The water supply of Colorado Springs comes from deep alpine lakes, down a mountain stream, then through pipes to deep reservoirs on a high mesa, and then through pipes to the city None of these would serve as breeding places for these larvae, and larvae which might wash into any of them—an unlikely thing of itself—would be drowned long before reaching the patient's residence Moreover, to suppose that such an extremely rare thing as a rat-tailed larva in the city water system could perform the practically impossible feat of coming through that system alive and would show up at precisely the right time following the taking of a vermifuge at a particular residence, is to strain even the very common credulity which people manifest in regard to coincidences as explanations of unusual things

While we have no such conclusive evidence as would be afforded by a case where the slop jar had actually been examined by a competent and skeptical person just before defecation, nevertheless, it seems more reasonable to regard this case as one of gastric or intestinal myiasis than as one of fraud or contamination The child had three good possible sources of infection and, by his own admission, habits that could easily lead to infection Carelessness in eating and drinking is more or less characteristic of children Flies of the family *Syrphidae* are abundant around the streets of Colorado Springs, and the following adult flies were collected there or nearby by Hall and Mr Horace Ragle, of Colorado Springs, during the summer of 1912 and determined by Mr Frederick Knab, of the U S National Museum *Eristalis tenax*, *E hurtus*, *Syrphus* sp, and *Eupeodes volucris* The relief after the passage of the larva is additional evidence and there is no possibility that the child was malingerer Five-

# THE INTERPRETATION OF THE NORMAL ELECTROCARDIOGRAM A CRITICAL AND EXPERIMENTAL STUDY \*

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## INTRODUCTION

Waller,<sup>1</sup> in 1888, was the first to demonstrate that the action currents arising from the heart muscle during its contraction were conducted out to the peripheral tissues in sufficient strength to be detected by leading off from the limbs to an electrometer. It was not, however, until the improvement and adaptation to physiological work of the thread galvanometer by Einthoven,<sup>2</sup> in 1903, that any considerable interest in this matter was aroused. In the nine years since Einthoven's first publication, a very large and rapidly increasing literature on the subject of the electrocardiogram has appeared, and great interest has developed as a result of its evident clinical and physiological importance. Notwithstanding the great amount of work that has been done, the various workers in this field are by no means agreed as to the interpretation of the normal electrocardiogram, and as a result, the interpretation of those departures from the normal that occur in cardiac disease, as well as the significance of the normal electrocardiographic curve in reference to the normal course of the cardiac impulse over the heart, has been largely influenced by the point of view held by the individual investigator.

Up to the present time the usefulness of the electrocardiogram from the clinical standpoint has been principally evident in the analysis of two classes of abnormal cardiac conditions, first, the heart arrhythmias, including under this the disturbances arising from depressed conductivity as well as those arising from ectopic impulse formation, and second, the condition and activity of the auricles (auricular hypertrophy, auricular fibrillation, etc). In these two classes of conditions the electrocardiogram has only certain technical advantages over the venous and esophageal pulse tracings.

In a third group of cases however, of great importance clinically and to which in its present development at least the venous pulse is not applicable as a means of study, namely, the functional activity of the

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1 Waller Philosoph Tr Royal Soc 1888, 178B, 215

2 Einthoven Ann der Physik, 1903, xii, 1056

ventricles, the electrocardiogram has yielded results which are to a considerable degree interpreted differently by different investigators. This is mainly due, it would seem, to the marked differences in interpretation of that portion of the normal electrocardiogram which represents ventricular activity (the Q, R, S and T waves of Einthoven). It is the purpose of the present paper to present certain facts from the literature and certain experimental observations of our own, which, while bearing on the interpretation of the electrocardiogram as a whole, have particular reference to the ventricular portion.

#### HISTORICAL REVIEW

An attempt at a complete review of the development of the electrocardiogram and the immense amount of clinical and experimental work of this subject would be beyond the scope of this paper. Reference will be made only to articles which bear directly or indirectly on the interpretation of its features as applied to the course of the cardiac impulse and the contraction of the different parts of the heart. An extensive review of the literature up to 1910 is given in the monograph of Kraus and Nicolai<sup>3</sup>.

The normal electrocardiogram, as described by Einthoven,<sup>4</sup> shows always at least three waves, all usually in the same direction. If the leads to the galvanometer are so arranged that a movement upward of the thread on the record occurs with relative negativity of the electrode in contact with that portion of the body more directly connected with the base of the heart, all of these three waves are in the upward direction. The three waves, according to the nomenclature of Einthoven, are designated P, R and T. With certain leads, T may be directed downward, and this wave may change its direction independently of the other waves in apparently normal beating hearts. Aside from these waves, two downward-directed waves may occur. The first of these (the Q wave of Einthoven) immediately precedes the R. It is quite infrequent and is regarded by Kraus and Nicolai<sup>3</sup> as abnormal. The second downward wave (the S wave of Einthoven) follows at once on the R. It is present in the electrocardiograms from adults in about one-third of all cases. In electrocardiograms from children it is always present and its frequency and size decrease with age (Kraus and Nicolai<sup>5</sup>). Finally, there are two parts of the curve which are described as having a horizontal course indicating equal potential of base and apex of the heart, one between the P and Q (or R) waves, the other between the R (or S) and T waves.

3 Kraus and Nicolai. *Das Elektrokardiogram des Gesunden und Kranken Menschen*, Leipzig, 1910.

4 Einthoven. *Arch internat de physiol*, 1906, iv, 132, *Arch f d ges Physiol*, 1908, cxxii, 517.

5 Kraus and Nicolai. *Berl klin Wehnschr*, 1907, lxiiv, 765 and 811.

In his first publication Einthoven ascribed the P and Q waves to the contraction of the auricles, the R, S and T waves to ventricular systole. Later work by Einthoven and others has shown that only the P wave of the normal electrocardiogram can be ascribed to the auricle. The P wave is the only wave present when the auricle alone contracts (Einthoven, Kraus and Nicolai). It is enlarged in auricular hypertrophy and absent in the absence of auricular contraction. The work of Samojloff<sup>6</sup> and of Kraus and Nicolai<sup>7</sup> tend to show that the P wave of the electrocardiogram is the first part of a diphasic variation which is evident in its entirety when the leads to the galvanometer are from the exposed auricle and not from the surface of the body.

In the interpretation of the group of waves which precede or accompany the first part of ventricular systole (Q, R and S), the views which have had widest acceptance are those of Einthoven and of Kraus and Nicolai. According to Einthoven,<sup>4</sup> the horizontal portion of the electrocardiogram following the auricular wave (P) and lying between this wave and the first ventricular wave, represents the time necessary for the impulse to pass through the His bundle and its various ramifications, where physiological connection is made with the ventricular musculature. During this time the galvanometer shows no movement, because both auricles and ventricles are at rest and the contraction wave through the connecting bundle is so weak as to cause practically no difference in potential. Einthoven evidently regards the passage of the impulse through the bundle to be associated with a weak contraction.<sup>7</sup> The next movement of the galvanometer thread does not occur, therefore, until the impulse has reached the ventricular musculature. The extensive branchings and connections of the auriculo-ventricular bundle, as shown by the work of Tawara,<sup>8</sup> ensure that the excitation passing downward from the auricles reaches the ventricle, not merely at the base or apex, but over a large surface of ventricular musculature. With the passage of the excitation into the ventricle the complex Q R S occurs. If the impulse first reaches the portions of the ventricles lying toward the apex, the apex of the heart shows relative negativity to the base, and the downward directed Q wave occurs. If other portions of the ventricles lying nearer the base (particularly the right ventricular base) first receive the

6 Samojloff *Beitr z Physiol u Pathol, Festschr f Hermann*, 1908, p 171, *Samml anat u physiol Vortr u Aufsätze* Hrgb von Gaupp und Nagel, 1909, 1-5

7 "Während dieser Zeit schreibt das Saitenbild des galvanometers eine horizontale Linie. Vorkammern und Kammern befinden sich in Ruhe, und die durch das Verbindungsbündel fortschreitende Kontraktionswelle ist an und für sich zu schwach um bei der für die Registrierung eines zweckmassigen Elektrokardiograms erforderlichen starken Spannung einen merkbaren Ausschlag des Galvanometers zu erzielen."

8 Tawara *Das Reizleitungssystem des Säugetierherzens*, Jena, 1906

impulse, the Q wave is absent. The R wave represents the spread of the excitation to and the contraction of the right ventricle and more basal lying regions. When S is present, it is an expression of the fact that the left ventricle and more apical regions of the heart soon show a predominant activity over the base and the apex thus becomes relatively electronegative to the base.

The second point of view, developed by Kraus and Nicolai,<sup>9</sup> rests on the well-known division of the ventricular musculature into the papillary system, the circular musculature (Treibwerk) and the outer spiral fibers (Nicolai<sup>9</sup>), the first two being in connection by the so-called intramural fibers. Following the contraction of the auricles the impulse passes over the His bundle and those structures functionally connected with it. The slow conduction in the bundle explains the long interval between the P and R (or S) waves, and no action current of any importance occurs at this time because of the small size of the muscular mass. After this interval the basal portions of the papillary system normally first receive the excitation and as an expression of this the curve rises sharply to form the R wave. The excitation now spreads toward the apex and the R wave ends. This spread of the excitation is largely in a linear direction and explains the large size of the R wave.

The potential differences arising under these circumstances are all in the same direction and are cumulative, while when many muscle masses passing in different directions are the seat of an excitation, the potential differences may to a considerable extent or entirely neutralize one another. The Q wave, when present, is an expression of the fact that the excitation passes in the Purkinje conducting system quite far toward the apex before it reaches the papillary muscles proper. This causes relative apical negativity for a short period. The papillary system includes the papillary muscles proper and the internal longitudinal fibers of the ventricles. Through the auriculo-ventricular conducting system and its ramifications the impulse is distributed to all parts of the papillary system. Normally the excitation reaches first that part of the papillary system lying toward the base and the true papillary muscles. The base of the ventricle thus shows relative negativity, and the R wave results without a preceding Q wave. The work of Hering<sup>10</sup> tends to show that the true papillary muscles are the first part of the ventricle to enter into contraction. Since these arise toward the apex of the ventricle, they do not form a part of the basal portion of the papillary system and this would seem to be opposed to the view of Kraus and Nicolai. Rehfisch<sup>11</sup> notes, however, that

<sup>9</sup> Nicolai. Verhandl. d. physiol. Gesellsch. zu Berlin, Nov. 22, 1907, Zentralbl. f. Physiol. 1907, vii, 678, Handbuch der Physiologie des Menschen. Hrgb. von Nagel 1909, i, 805.

<sup>10</sup> Hering. Arch. f. d. ges. Physiol. 1909, cxxvi, 225.

<sup>11</sup> Rehfisch. Deutsch. med. Wchnschr., 1910, xxxvi, 977 and 1035.

the basal portion of the papillary system is more or less firmly fixed by attachments to the aortic cartilage and the auriculoventricular ring, and while this part probably receives the first branches from the His bundle and normally is the first part of the ventricle to receive the excitation, the first part to show movement of sufficient degree to be graphically recorded may well be the true papillary muscles. The basal portions of the papillary system may thus enter first into excitation, but due to the anatomical arrangement, show no visible contraction. Kraus and Nicolai thus conceive of the excitation as spreading out through the His bundle and its ramifications to various parts of the internal longitudinal fibers and papillary muscles of the ventricles. Normally, it affects the basal portions first, and hence the first ventricular wave (R) is directed upward. When the excitation reaches the parts of the papillary system lying more toward the apex of the ventricles, the true papillary muscles receive the impulse at their base and it spreads from base to apex of these muscles, a course opposite in direction to that from base to apex of the ventricle as a whole. This causes a downward-directed wave (Q), a wave stated by Kraus and Nicolai to be absent from the strictly normal electrocardiogram. In such an event, however, the activity of the base soon becomes predominant and the R wave occurs. The R wave is completed when the excitation spreads out from the papillary system through the intramural fibers to the circular fibers (*Treibwerk*) of the ventricles. If the excitation in its spread from the base reaches the apical parts of the papillary system before this occurs, as is usually the case, a short period develops in which there is relative negativity at the apex. This is expressed as the S wave. If, on the other hand, the spread through the intramural fibers occurs before or simultaneously with the excitation reaching the apical parts of the papillary system, the S wave is absent.

It will be seen that considered broadly, the views of Einthoven and of Nicolai in reference to the cause of the Q, R and S waves of the electrocardiogram agree quite closely. No distinction is made in either between the spread of excitation and contraction of the muscle, and it would seem that it is really contraction of the different regions which causes the development of the electrocardiogram. Einthoven even suggested, as we have seen, that the spread of the impulse through the auriculoventricular bundle is associated with a weak contraction. According to both views this passage through the bundle and conductive system of the heart produces no wave in the electrocardiogram. It is only when the larger muscle masses of the ventricle are affected that any noticeable differences in potential arise. The two views differ mainly as to exactly what muscular masses of the ventricles in their activity produce these differences in potential. Einthoven lays stress particularly on the right ventricular base in the production of the R wave, while Nicolai goes into more detail in reference to the different layers of muscle of the ventricles.

Passing now to the remaining portions of the electrocardiogram, the horizontal part lying between the R (or S) wave, and the T wave, and the T wave itself, both Einthoven and Nicolai explain the former on a general and simultaneous contraction of the musculature of both ventricles, the action currents arising therefrom neutralizing one another so that no difference in potential between base and apex is present Nicolai lays particular stress on the contraction of the circular fibers (*Treibwerk*) The development of the T wave is explained by Einthoven by the right ventricle (particularly the basal part) remaining in contraction longer than the remainder of the heart, causing the development of a late negativity of the base This view is founded on the experimental work of Bayliss and Starling,<sup>12</sup> concerning the course of the excitation over the mammalian ventricle These investigators concluded that in the exposed dog's heart the impulse passed from base to apex, and the indication of terminal basal negativity in the electrocardiogram (recorded by the capillary electrometer from the exposed heart) was to be explained by the base remaining in negativity after the negativity had subsided at the apex and not to a return of the excitation to the base If under abnormal conditions the contraction ceases in each ventricle simultaneously, as Einthoven supposes to occur in myocardial insufficiency, the T wave is entirely absent Kraus and Nicolai, on the other hand, explain the T wave as due to a late return of negativity to the base of the heart, a region of the base lying especially around the aorta and pulmonary artery being the last portion of the ventricles to enter into contraction This view of the course of the impulse was first suggested by Gotch<sup>13</sup> in 1907, and elaborated in more detail in 1909. Gotch conceives the contraction of the ventricle as beginning around the venous orifices, at the base of the ventricle, and spreading to the apex and thence to the arterial bases of the ventricles, following in its course the direction of the primitive cardiac tube This work will be considered more fully in a detailed discussion as to the course of the T wave later in this paper

Of other views that have been advanced to explain the normal electrocardiogram, we may next consider the interpretation of Eppinger and Rothberger<sup>14</sup> As we have seen, both Einthoven and Nicolai explain the electrocardiographic curve as a resultant of the play of antagonistic forces of electric potential between base and apex Eppinger and Rothberger object to Einthoven's assumption that the relatively weak right ventricle can be regarded as representing, so far as the electrocardiogram is concerned, the cardiac base, and playing the predominant rôle in the production of the normal curve, while the left ventricle with its massive

12 Bayliss and Starling Internat Monatsschr f Anat u Physiol, 1892, ix 256 and 276

13 Gotch Proc Royal Soc, 1907, 79B, 323, Heart, 1909, 1, 235

14 Eppinger and Rothberger Wien klin Wchnschr, 1909 XLII, 1091



basal region, is actually regarded as the cardiac apex in this scheme Eppinger and Rothberger understand Nicolai to regard the R wave as an expression of the spread of the stimulus, to conduction of the impulse in contrast to actual contraction, and cite several facts which they regard as opposed to such an interpretation. They state that if R is referred to conduction alone the interval from P to the end of R, which under these circumstances would represent As-V's conduction, is actually larger than this conduction period. They find it difficult to understand why the R wave is not always diphasic in such conduction in a linear direction between two points and why the conduction of the excitation produces such a marked effect (R wave) in the terminal connections of the conductive system while it produces no effect in its passage through the bundle and its branches. They believe that the observations of Kahn on the time relation between the R wave and the rise of intraventricular pressure do not support, as they have been supposed to do, Nicolai's interpretation. Kahn in a series of papers, has studied the time relations between the waves of the electrocardiogram and various features that occur in the cardiac cycle. He found by simultaneous records of the intraventricular pressure the carotid pulse and the electrocardiogram, that the R wave begins before the pressure in the ventricle rises and is completed during the period of tension, having ended by the time the outflow period begins.<sup>15</sup> Since, according to Nicolai, the R wave is due to the activity of the papillary system, it must occur before that part of the heart musculature which causes a reduction of the internal capacity of the heart becomes active, and this, as we see, Kahn finds to be the case. Similar relations have been found by Kahn to hold between the beginning of the first heart sound and the R wave.<sup>16</sup> Eppinger and Rothberger criticize those facts as applied in support of Nicolai's view, in that they believe that the electrical change actually in all cases precedes the mechanical change to which it corresponds, and call attention to the fact that Kahn's curves show that the P wave of the electrocardiogram also precedes the rise in the pressure curve of the right auricle. Furthermore, they state that the contraction of the musculature must reach a certain point before rise of intraventricular pressure begins. They cite the experiment of Kahn in which he found that in artificial stimulation of the ventricle in vagus standstill the action current began 0.75 seconds before the rise of intraventricular pressure. Here the contractile substance was directly stimulated and yet the mechanical definitely followed the electrical response. Kahn,<sup>17</sup> in reply to these objections, shows by a series of experiments on the dog's heart that while the electrical latent period of the heart (the time from incidence of stimulus to electrical

15 Kahn Arch f d ges Physiol, 1909, cxxvi, 197

16 Kahn Arch f d ges Physiol, 1909, cxxix, 291

17 Kahn Arch f d ges Physiol, 1910, cxxxii, 209

change) comprises a considerable period of time (0.2 to 0.3 seconds), the difference between the electrical and mechanical response is extremely short, not more than 0.02 seconds. Kahn concludes from this that the mechanical contraction of that part of the heart, the electrical expression of which goes to form the R wave, must occur not later than 0.02 of a second after this wave begins. He repeats his original conclusion as to the relation of the R wave to activity in the ventricle and shows that the mechanical activity of the anterior wall of the right ventricle begins after completion of the R wave. The time relations of the rise in pressure in the left ventricle, the first heart sound and the mechanical activity of the wall of the right ventricle to the beginning and length of the R wave of the electrocardiogram confirms the view that the R wave is to be referred to the activity of the papillary system. Kahn further states that he has never committed himself to the view that the R wave is purely a conduction phenomenon, but has merely insisted that the activity of the circular fibers (*Treibwerk*) occurs only after the completion of the R wave and has nothing to do with the production of this wave. Rehfisch<sup>11</sup> calls attention to the fact that Eppinger and Rothberger have really misinterpreted Nicolai's statement in reference to the R wave. Nicolai does not state that the R is a pure conduction wave, but that it arises from conduction in and contraction of one of the muscle layers of the heart, namely, the papillary system. It is extremely difficult to obtain from Nicolai's statements the relative parts he regards conduction and contraction to play, if indeed he has in mind any sharp distinction between the two.

Having found serious objections to the two prevalent theories concerning the interpretation of the electrocardiogram, Eppinger and Rothberger present another point of view founded on a long series of experiments in which they attempted to render functionless different layers of the heart muscle by freezing with ethyl chlorid or by the injection of mercuric chlorid or silver nitrate. The results from these experiments lead them to the conclusion that it is not the play of antagonistic electric potentials at the base and apex of the ventricles that produce the electrocardiogram, but that the curve is the resultant of the action currents arising from the longitudinal and circular muscle system of the heart. Activity of the longitudinal musculature causes the galvanometer to give an upstroke (when connected so that the R is directed upward), while activity of the circular fibers neutralizes this or actually produces a downward movement. In other words, the production of the electrocardiogram does not depend on the resultant of electric conditions developed at base and apex of the ventricles from activity of the muscle in these regions, as assumed in the theories of Einthoven and of Kraus and Nicolai, but whether the curve is up or down depends on whether negativity pre-

dominates in the longitudinal or circular fibers of the heart. This conclusion is founded on the following experimental results:

1 Freezing the surface of the ventricles with a spray of ethyl chlorid produces no change in the R wave. This is true for both ventricles and for base and apex. The R wave must arise, therefore, from some deeper structure than the outer longitudinal layer. The T wave becomes smaller or negative on freezing any part of the surface of the left ventricle or the surface of the apex of the right ventricle. Freezing the surface of the base of the right ventricle, on the other hand, increases the T wave (in a positive direction). Section shows that the effect of freezing does not extend at the greatest to a depth of more than 1 millimeter.

2 Injury to the deeper layers of the left ventricle by injection of mercuric chlorid or silver nitrate caused in certain cases increase in the height of R, abolition of S, if present, loss of the level period between R and T, increase of the height and duration of T, and finally fusion of R and T to form a large monophasic upward directed curve. This effect, regarded as typical, was observed in thirteen out of twenty-five cases. In some cases no effect occurred from the injury, in others, there was merely an increase of T and a tendency to fusion with R. The results were the same whether the injections were made into the base or the apex of the ventricle. Injury to the anterior and posterior papillary muscles produced no effect.

3 Injury to the deeper layers of the right ventricle cause in typical cases the appearance, or increase if already present, of the S wave and increase of the T wave. The S and T continue to increase, the R wave becomes reduced and finally disappears and the curve assumes the form characteristic of an extra-systole of the left ventricle. That it is not, however, an extra-systole of the left ventricle is shown by the presence of a P wave. In some cases the R is reduced, the T increased and S is unaffected, but usually the essential change is the appearance or increase of an already present S wave. It is suggested that the different effects observed may be due to differences in the seat of injury, particularly as to whether the auricular or pulmonic regions are affected, but the experiments are not sufficient to demonstrate this.

4 Injury to the interventricular septum causes the same effect as injury to the deep layers of the left ventricle, unless the lesion reaches the muscles lying just beneath the endocardium, when the result is the same as that following injury to the right ventricle.

Eppinger and Rothberger cite the anatomical researches of Krehl and others as showing that while the middle or circular layer of fibers (*Treibwerk*) of the right ventricle is very poorly developed, it forms the greater mass of musculature of the left ventricle. The longitudinal fibers, on the other hand, are well developed in both ventricles. They believe, therefore, that any effect produced by injury to the deeper layers of the

left ventricle can be referred mainly at least, to the circular fibers. Injury to these causes an increase in the whole electrocardiogram in an upward direction, while injury to the right ventricle or internal longitudinal layers of the septum or left ventricle causes the opposite effect. The antagonistic forces at work in the production of the electrocardiogram may thus be regarded as the circular and longitudinal muscular systems. The former in its activity tends to cause the electrocardiographic curve to descend, the latter acts in the opposite direction. The normal electrocardiogram represents the resultant of these two. When one set of fibers is injured, the action of the other preponderates and a corresponding change in the curve occurs.

Eppinger and Rothberger's detailed explanation of the electrocardiogram is as follows. The R wave is an expression of the unopposed action of the internal longitudinal fibers and corresponds therefore to the onset of systole of the ventricles. The remainder of the electrocardiogram is the resultant of the action of two forces. The activity of the circular fibers may predominate for a short time to form an S wave. The level part of the curve between S (or R) and T represents a complete antagonism of the two systems. They make no definite statements in reference to the formation of the T wave. The observation of Einthoven that in man hypertrophy of the left ventricle is frequently associated with a negative R, while in hypertrophy of the right ventricle the R is increased in a positive direction, seemed to support his view that the base of the heart, so far as concerns the production of the electrocardiogram, is represented by the right ventricle and it is the activity of this which normally causes the R wave. Eppinger and Rothberger note that the same fact may be well explained on their interpretation, since in left ventricular hypertrophy the increase is almost entirely in the circular fibers, while in right ventricular hypertrophy it is the longitudinal system which is increased.

In a later paper, Eppinger and Rothberger<sup>18</sup> study the effect on the electrocardiogram of dogs of cutting away the whole of either the right or the left ventricle. Complete removal of the left ventricle causes the normal electrocardiogram to be replaced by a large upward-directed monophasic curve, which persists until stoppage of the heart (usually in about five minutes). The first effect of removal of the right ventricle is a reduction of the R and a great increase in the S wave, but before complete stoppage of the heart the curve assumes a fairly close resemblance to the normal electrocardiogram. The R wave is small, the T very large. It would appear, therefore, that the left ventricle alone can give an approximately normal electrocardiogram, while the right ventricle alone cannot. Since the left ventricle contains both longitudinal and

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18 Eppinger and Rothberger. *Zentralbl f Physiol*, 1911, xxiv, 1053

circular musculature, while the right ventricle contains very few if any circular fibers, these results seem to bear out the interpretation based on their earlier work

Eppinger and Rothberger thus assign all the waves of the electrocardiogram, more definitely perhaps than either Einthoven or Nicolai, to muscular contraction. The accuracy of their experiments and the value of the conclusions derived from them would seem to depend largely on the exactness of localization of the methods employed for producing loss of function in the different muscle layers. The injury done was apparently determined as far as possible by post-mortem examinations. It must be noted that the experimental results were by no means uniform and many departures from the results they regarded as typical occurred. These may be perhaps explained, as they suggest, by injury to more than one layer. The heart of the frog and tortoise, as shown by Samojloff,<sup>19</sup> Straub,<sup>20</sup> and Gotch,<sup>21</sup> gives an electrocardiogram in every way similar to that of the mammal. We have been unable to find in the literature any full description of the muscular layers of the cold-blooded heart or any study as to the possible differentiation into longitudinal and circular fibers. It is impossible, therefore, to say at present whether the similarity of the electrocardiogram of cold-blooded animals and mammals is opposed to the theory of Eppinger and Rothberger. They suggest that this similarity is best explained on a similar anatomical arrangement of the cardiac musculature in the cold-blooded animal and the mammal.

From results obtained by the action of digitalis on the dog's heart *in situ*, Selenin<sup>21</sup> interprets the electrocardiogram as the resultant of the interference of the electrical waves arising from the right and left ventricles respectively. The ground elements are the diphasic waves of the two ventricles, such as occur in characteristic and unmodified form in extra-systoles of these chambers. An extra-systole of the right ventricle produces a diphasic electrocardiogram in which the first movement (R) is upward, the second (T) downward. The R is large, the T relatively small. An extra systole of the left ventricle, on the other hand, causes a diphasic curve in which the first movement is downward, while the T is positive. The R in this case is smaller than the T. Combining these two curves one may obtain a curve similar to the normal electrocardiogram of the two ventricles. The upward R of the right ventricle more than neutralizes the downward R of the left, therefore the normal R is positive in direction, but smaller than the R of a right ventricular extra-systole. The positive T of the left ventricle is also larger than the negative T of the right ventricle, so the T wave of the normal electrocardiogram is usually in an upward direction. Selenin explains the effect of

19 Samojloff Arch f d ges Physiol, 1910, cxxxv, 417

20 Straub Ztschr f Biol, 1910, lxxi, 523

21 Selenin Arch f d ges Physiol, 1912, cxliii, 137

digitalis as causing a preponderance in action of the left ventricle and quotes from the literature in support of the view that digitalis acts mainly on the left ventricle. In the therapeutic stage of action of the drug the P and R are not essentially changed, while the T is increased. As the toxic stages develop the R wave becomes reduced, the T much increased and finally the curve resembles that caused by an extra-systole of the left ventricle. The R almost entirely disappears, it is followed by a large downward-directed wave (S) and a large positive T. The S wave is explained by Selenin by an absence of complete synchronism of the electrical curves of the two ventricles, the S wave really representing the first phase of the diphasic curve of the left ventricle.

Opposed to Selenin's view may be mentioned the observation of Eppinger and Rothberger,<sup>18</sup> that the left ventricle alone may give an approximately normal electrocardiogram, while the right ventricle alone cannot. Eppinger and Rothberger<sup>22</sup> have furthermore shown that when the branch of the His bundle going to either ventricle is cut, the electrocardiogram assumes the form characteristic of an extra-systole of the ventricle still retaining its connection with the bundle. Both ventricles continue to contract and yet the electrocardiogram is profoundly modified. The development of the so-called atypical electrocardiogram characteristic of extra-systoles would seem to depend, therefore, rather on an abnormal entrance of the impulse into the ventricle. Instead of the excitation being conducted to the ventricle over its normal route from the auricle, the His bundle and its branches, it originates at the part of the ventricular muscle stimulated, or in Eppinger and Rothberger's experiments, spreads from the other ventricle. When one ventricle is stimulated, both, of course, contract, and there is no evidence that the one not directly stimulated contracts less strongly than the one stimulated. To support Selenin's view, it would seem necessary to show that the left ventricle contracting alone or the right ventricle contracting alone would give curves, which, on combining, would form the usual electrocardiographic curve as a resultant.

In marked contrast to the preceding views as to the interpretation of the electrocardiogram, is the theory of Hoffmann.<sup>23</sup> From a critical review of the literature, certain observations in man and experimental work on animals, Hoffmann came to the conclusion that the normal electrocardiogram represents two distinct activities in the heart occurring during its systole, namely, conduction of the excitation and contraction of the muscle. Each activity according to this interpretation, is associated with the development of electrical energy, and so far as the ventricle is concerned, the Q R S complex is caused by the passage of

<sup>22</sup> Eppinger and Rothberger. *Zentralbl f Physiol*, 1911, xxiv 1055. *Ztschr f klin Med* 1910 lxx, 1.

<sup>23</sup> Hoffmann. *A. Arch f d ges Physiol* 1910, cxviii, 552.

the wave of excitation over the conducting system of the ventricle, while the remaining portion of the ventricular electrocardiogram (level period and T wave) results from the electrical energy liberated by the contracting ventricle. That a possible separation of these two phenomena in the genesis of the electrocardiogram must be considered seems to have been first suggested by Judin.<sup>24</sup> The curve of electrical response of a frog's skeletal muscle (gastrocnemius) shows, according to Judin, a rapid and large wave preceding and a much slower and less intense change accompanying the contraction of the muscle. Judin evidently realized the importance of this observation in reference to the analysis of the electrocardiogram, but so far as we know he has not attempted this in detail. In the article referred to the following statement occurs:

Dem Aussehen nach erinnert diese Kurve sehr an den Teil des Elektrokardiogramms, der sich auf die Ventrikel bezieht. Daraus folgt, das ehe eine Erklärung des Elektrokardiogramms gegeben wird, es geboten erscheint, Klarheit in die Frage von den Aktionsströmen des Muskels überhaupt zu bringen, da diese Frage nicht so einfach ist, wie man dies bis jetzt gewöhnlich annimmt.

Hoffmann shows by a review of the literature and by his own experimental work that the R and T waves frequently vary independently of each other, and believes that the R wave cannot be considered as representative of contraction of the ventricular muscle, since it does not, as has been assumed, especially by Einthoven, show any relation in its size to the extent of this contraction. He calls attention to the fact that in the so-called atypical electrocardiogram (electrocardiogram of extrasystoles or ectopic impulse formation<sup>25</sup>) the R wave is much larger than the normal, while in many cases at least the mechanical systole is much weaker than normal. Many observations, on the other hand, indicate that the size of the T wave, frequently, at least, varies directly with the size of contraction.

The T wave is increased during and after muscular work (Einthoven,<sup>4</sup> Muller and Nicolai<sup>26</sup>), it is first increased and then decreased by the action of heart poisons (Kraus and Nicolai<sup>3</sup>), before death it becomes small or disappears (Kraus and Nicolai), and it is small or negative after excessive hemorrhage and in chloroform narcosis (Einthoven<sup>4</sup>). Hoffmann's own experiments speak strongly for the view of direct association between the contraction and the T wave. He recorded the electrocardiogram from frog hearts simultaneously with suspension curves of the ventricle and showed that when the heart is brought to a complete standstill by the application of muscarin, an electrocardiogram is still evident

<sup>24</sup> Judin. *Zentralbl f. Physiol.*, 1908, **xxii**, 365.

<sup>25</sup> Hering has introduced the term *nomotopic* to indicate a normal impulse originating in the normal position of the sinus region. All impulses originating outside of this area are *ectopic*.

<sup>26</sup> Hering. *Arch f. d. ges. Physiol.*, 1910, **cxxxvi**, 466.

<sup>26</sup> Muller and Nicolai. *Zentralbl f. Physiol.*, 1908, **xxii**, No. 2.

This electrocardiogram from the non-beating heart differs from the normal merely in the absence of a T wave, the R wave is not reduced in size. As the beats return following the removal of the muscarin effect by the application of atropin, the R wave becomes no greater, although the extent of contraction increases rapidly. The T wave, however, reappears, and gradually increases as the size of the beat returns to normal. In the frog's heart during *treppe* the R wave does not increase as the extent of contractions increase. Application of distilled water to the heart produces weaker and weaker systoles and finally cessation of contraction without decrease in the R wave, but with decrease and disappearance of the T wave. These results show a striking lack of correspondence between the extent of contraction and the R wave and prove that the production of the electrocardiogram is in part unconnected with contraction of the cardiac muscle. The abolition of contraction with maintained conductivity does not entirely abolish the electrocardiogram. The group R (Q, R, S) is to be ascribed, not to contraction of the muscle, but to conduction of the cardiac impulse. Under normal condition the impulse wave, or wave of excitation, is followed by the contraction wave. Under certain experimental conditions, as described above, this does not occur and the change in the electrocardiogram that results is confined solely to the T wave. Hoffmann further notes that in the frog's heart the T wave falls toward the end of systole, and when the length of systole is changed by cooling or warming the heart the T wave separates or approaches R to hold its place always toward the end of systole. The T wave is thus closely associated with contraction and particularly the latter part of the curve. Hoffmann agrees with Einthoven and with Kraus and Nicolai in explaining the level part of the electrocardiographic curve between R and T as due to simultaneous contraction of all parts of the heart and the action currents arising from this neutralizing one another so that no difference in the potential of base and apex occurs. His interpretation of the T wave is essentially that of Einthoven in that it is referred to the cessation of contraction in certain regions of the ventricle while contraction continues in other regions. With reference to each wave of the electrocardiogram the interpretation in detail is as follows. The P wave is the expression of the spread of the impulse over the auricle. The following level part of the curve between P and R represents the contraction of the auricle and the passage of the impulse through the His bundle to the ventricle. The contraction of the auricle is presumably too weak to give any noticeable differences in potential, and hence no auricular T wave is normally present. The conduction through the His bundle is very slow and this explains why it produces no effect on the electrocardiogram. He cites the work of Grützner, Mackenzie, Kuhe and Biedermann, in showing the absence of electrical change in slowly contracting smooth muscle. The impulse is distributed



first to the papillary muscles. If the parts lying near the apex first receive the impulse from the branches of the bundle, a Q wave occurs. When the excitation reaches the base the R wave occurs. It then rapidly passes to the apex, causing the development of the S wave. By the end of this period the whole musculature of the heart has received the wave of excitation. Now contraction sets in and for a certain period no further change occurs in the electrocardiogram, because all of the heart muscle is active. After a time contraction begins to wane in certain regions and persists undiminished in others and thus gives rise to a difference in potential between base and apex and the T wave is produced.

The essential characteristic of Höffmann's interpretation and the point in which it differs from all views in reference to the formation of the electrocardiogram is thus the sharp differentiation between the rôle played in its production by conduction of the excitation on the one hand and the contraction of the muscle on the other. As expressed by Höffmann, the electrocardiogram is to be regarded as a curve of excitation plus the end of a contraction curve.

Considering now in more detail the interpretation of the T wave, the various views that have been more or less definitely expressed may be divided into four groups. (1) The T wave is not really indicative of any potential change arising from activity of the cardiac muscle, but is due to changes in the position of the heart during its contraction, resulting in disturbance of the null point of the galvanometer. (2) The T wave is the result of the contraction of the musculature of certain regions or certain layers of the heart just as the R wave is the expression of the contraction of other regions. (3) The T wave is not a special feature associated with the contraction of musculature from any particular region of the heart, but is a phenomenon associated with contraction of cardiac muscle in general. (4) Some factor or factors enter into its formation other than simple contraction of the muscle.

The first mentioned view has been suggested by Ussif<sup>27</sup>. As a result of contraction of the ventricle the long axis increases and a change of the line of isopotential in relation to the leads to the galvanometer results. Normally this change in position results from activity of the left ventricle and the T wave is positive. If the right ventricle contracts more strongly than the left the T wave is negative. If the whole heart contracts weakly, as occurs in dilatation, the form change is slight or absent, and the T wave is likewise small or absent. Most authors have attempted to interpret the T wave according to the second mentioned view. Probably the interpretation that has been most widely accepted is that developed by Gotch<sup>13</sup>. In this the T wave is referred to a late contraction of the muscular re of the ventricles surrounding the base

27 Ussif. Quoted from Rehder'sh (Note 11)

of the aorta and pulmonary artery Gotch attempts to bring the course of the cardiac impulse into relation with the phylogenetic development of the heart from the primitive cardiac tube, and conceives the impulse in the fully developed mammalian organ as entering the auricular end of the ventricle, thence passing to the apex and finally terminating at the arterial base (aortic and pulmonic bases) Bayliss and Starling<sup>12</sup> had previously worked on the course of the impulse over the mammalian ventricle by the method later used by Gotch and had concluded that the late basal negativity (as shown by the T wave of the electrocardiogram) was due, not to return of negativity from the apex to the base, but resulted from the fact that the negativity at the base outlasted that at the apex They conceived the contraction wave as beginning at the base and passing to and terminating at the apex, while Gotch differentiates between the auricular and arterial bases and supposes the wave of contraction to pass from the first to the apex and thence to the aortic and pulmonic base Gotch worked on the exposed heart of the tortoise and rabbit with the electrodes placed directly on the surface of the heart and connected with a capillary electrometer With one electrode in contact with a considerable part of the base of the ventricle, including the muscle lying around the base of the aorta, the other in contact with the apex, he obtained a curve from the tortoise's heart resembling the normal ventricular electrocardiogram with a pronounced T wave The late negativity of the base (T wave) was not obtained when the basal contact was limited to the lateral regions of the ventricular base, while a localized contact on that part of the base from which the aorta arises gave a curve resembling that obtained when the contact included the basal region as a whole It seemed clear, therefore, that the portion of the base which is responsible for this late negativity is the region lying at the base of the aorta The base of the ventricle is thus the seat of two potential changes which occur at different times in ventricular systole, one early, the other late The second change, that which gives rise to the T wave, is only manifest when the contact of the basal electrode includes that portion of ventricular musculature lying at the root of the aorta If it is true that the impulse passes as a wave from the auriculoventricular junction to the apex and then returns to the neighborhood of the aorta, the former should show evidence of negativity before the aortic region, and this he found actually to be the case When one electrode was placed in contact with the lateral parts of the ventricular base and the other with the base of the aorta, the curve obtained was diphasic, the auricular base was first negative and after a period of equipotential, relative negativity developed at the aortic region The experiments on the exposed heart of the rabbit confirmed this interpretation Gotch, furthermore, found that in the frog, tortoise and rabbit, an increase in the contraction of the aortic region of the ventricle produced by a rise of blood-pressure is associated with an

increase in the size of the T wave. In the rabbit's heart a weakening of the beat of the ventricle from any cause results in a decrease, or if pronounced, a total disappearance of the T wave. In a strongly-beating rabbit's ventricle shifting the basal electrode away from the aortic (or pulmonic) region results likewise in a reduction of the T wave.

Nicolai, as we have seen, explains the T wave by a return of negativity to the base and hence agrees with the interpretation first proposed by Gotch. Einthoven, on the other hand, inclines to the conception developed by Bayliss and Starling, that the terminal basal negativity does not represent a return but a continuation of negativity of this region after it has disappeared at the apex. Eppinger and Rothberger make no very definite statements in reference to the cause of the T wave. They note that since freezing the superficial layer of the ventricular muscle affects only the T wave, while injury to the deeper layers produces none or only a slight effect on this wave, it probably does not arise from activity of the deeper layers. In their description of the effects of injury to the deeper muscles they, however, describe quite marked effects on the T wave.

The third point of view mentioned above, namely, that the T wave is not to be referred to any special region or layer of musculature, but is an essential feature accompanying the contraction of cardiac muscle in general, is the central idea in Hoffmann's interpretation of the electrocardiogram. Hoffmann, as we have seen, differentiates sharply between the electrical effect produced by conduction, on the one hand, and contraction on the other. The first is represented in the ventricular electrocardiogram by the group R (Q, R, S) the second by T. Early in systole, when the whole cardiac muscle is in contraction, no T wave normally develops because the various action currents produced neutralize one another so that no difference in potential between base and apex is present. Such difference in potential only arises when some portion of the heart (normally the apical regions) begin to pass out of contraction, while others (normally the basal regions) remain strongly contracted. While thus it is really one particular region of the heart, the ventricular base, which is mainly concerned in the production of the T wave, by this point of view as expressed, any contracting cardiac muscle, no matter from what region of the heart, should give a T wave if the change in potential thereby induced is unopposed by simultaneous changes developed in other regions of the heart.

Finally, the view that some other factor besides simple contraction of heart muscle plays a rôle in the formation of the T wave has been suggested by Samojloff and by Straub. Samojloff,<sup>19</sup> working on the frog's heart, came to the conclusion that the T wave is composed of two components, one representing conduction of the excitation, the other contraction of the muscle. He found in extra-systoles of the frog's ventricle

that while the direction of the R wave changed, depending on whether the extra-systole arose from base or apex stimulation, that the T wave always retained the direction present in the normal beat. However, size of the T wave varied in these two cases. When the T wave in extra-systole is in the same direction as the R, it is smaller than in normal beat, while when the T is in opposite direction to the R, it is larger than the normal. This can be explained if the T wave is regarded as representing the second part of a diphasic curve of conduction, parallel to a contraction curve, in which the latter element always predominates. The part of the T representing conduction is always opposite to the direction of the R, while the part representing contraction is in the same direction as it does, the second part of a diphasic change. When the second component of the T (representing contraction) is opposite in direction to this, these two subtract from each other and the T is small. When they are both in the same direction the two components are added and the T wave is larger than normal. It will be noted that in each case the second component of the T (that representing contraction) predominates. Straub<sup>20</sup> places the T wave at the beginning of diastole in the frog's heart and suggests that it may be in some way connected with assimilatory processes in the muscle. He showed that warming the ventricle increases its size (in a positive direction), while cooling causes it to become small or negative.

The T wave, as has been noted by most writers, is by far the most variable feature of the electrocardiogram. While in the normal curve from man it is nearly always in the same direction as the R wave, in the frog, tortoise and in mammals used in experimental work a downward directed (negative) T wave is not at all uncommon in an apparently normal heart beat. Many observations have been made in an attempt to determine the factor or factors that underlie the variations in size of the T wave and the majority perhaps point to the conclusion that a close correspondence exists between the extent of ventricular contraction and the size of this wave. The work of Hoffmann in this connection and the literature he cites has already been referred to. Rehfisch,<sup>28</sup> in an extensive study as determined by orthodiagraphic methods. The highest positive T waves come essentially to this conclusion. In an analysis of 350 clinical cases the size of the T wave was compared with the arterial blood-pressure measured by the v. Recklinghausen tonometer and the size of the heart as determined by orthodiagraphic methods. The highest positive T waves were present in cases of moderate blood-pressure (111 to 130 mm. systolic pressure), and in which there was no great enlargement of the heart, but in which the x-ray examination showed particularly strong heart movement. The most pronounced examples of this type were cases of well developed hypertrophy with no evidence of broken compensation, es-

cially well marked in cases of pure cardiac neuroses. In pronounced heart weakness or in dilatation and in very small hearts with low blood-pressure, the contractions of the heart, as shown by the fluoroscope, are small, and these are always associated with a small T wave. In greatly enlarged hearts with very high blood-pressure (180 to 250 mm systolic) the T wave is small or negative in the majority of cases. The R wave shows a tendency to increase in size with increase in blood-pressure and increase in size of heart, but the change is not so marked as occurs in the case of the T wave. Pribram and Kahn<sup>29</sup> conclude from a study of over 300 pathological cases that while variations in the size of the T wave in apparently similar cases is quite common, in general T is strongly positive in forcibly contracting hearts, while it is small or absent in very weak hearts. While they find that frequently the R wave is modified in right and left ventricular hypertrophy in the way described by Einthoven, many exceptions occur. Samojloff<sup>30</sup> found that in the electrocardiogram of the frog's heart the first systole following the compensatory pause of an extra-systole produced by stimulation of the ventricle ("post extra-systolic systole") shows a larger T than normal, while the R wave is unchanged in size. The T wave of the second normal systole following an extra-systole is however, smaller than that of succeeding systoles. Langendorff<sup>31</sup> and Bottazzi<sup>32</sup> have shown that the first post extra-systolic systole is larger, the second smaller, than the average systole. In the electrocardiogram these changes in size of systole are marked solely by changes in size of the T wave. Moreover, in the extra-systole itself the T wave is smaller than normal and this difference is more pronounced the earlier the extra-systole follows a normal systole. As is well known, the earlier an extrasystole falls in the preceding cycle the smaller the contraction. The size of the extra-systolic contraction is thus directly connected with the size of the T wave. That the T wave frequently varies independently of the R and seems to depend as to degree of its development largely on the extent of contraction of the heart, is further indicated by studies on the action of certain poisons on the heart and on the influence of the extrinsic cardiac nerves.

The action of drugs of the digitalis series has been studied by Nicolai and Simons,<sup>32</sup> by Straub,<sup>33</sup> and more recently by Selenin.<sup>21</sup> The last-named investigator worked on dogs with hearts *in situ* and found that in the stage of therapeutic action of digitalis the P and R waves were not essentially changed from the normal, while the T wave was increased in size. Nicolai and Simons describe in man an increase in size of the T

29 Pribram and Kahn. *Deutsch Arch f klin Med*, 1910, *xcix*, 479.

30 Langendorff. *Arch f d ges Physiol*, 1898, *lxx*, 473.

31 Bottazzi. *Zentralbl f Physiol*, 1896, *v*, 401.

32 Nicolai and Simons. *Med Klin*, 1909, *v*.

33 Straub. *Ztschr f Biol*, 1909, *lvi*, 106.

wave without essential change in the R as a result of therapeutic doses of digitalis. Straub describes similar effects from strophanthin in cats and rabbits at the beginning of the toxic stage of action. Further action causes a negative T. Epinephrin (adrenalin) causes the T to become large and negative. The increase of the T is the characteristic effect of the action of digitalis on the frog's heart, according to Straub<sup>34</sup>. Hering,<sup>34</sup> in studying the *pulsus alternans* produced by the intravenous injection of glyoxylic acid, found that the most common change in the electrocardiogram produced by the ventricular alternation is in the T wave, the R wave is never alone affected and is always less changed than the T. In a previous paper, Hering<sup>35</sup> had shown that the essential feature in the alternation produced by glyoxylic acid in the mammal's heart is not a hyposystole (diminished contraction) of the whole ventricle but a partial asystole. Certain parts of the ventricle do not enter into contraction at all in the alternating small beats. The view that *pulsus alternans* is a hyposystole seems to have been first suggested by Gaskell,<sup>36</sup> and to have been confirmed for the frog's heart by Trendelenburg,<sup>37</sup> and by Muskens<sup>38</sup>. Hering could find no relation between the portion of the ventricle affected and the change in the T wave and concludes that the T wave is produced by every part of the musculature which may be in activity toward the end of systole and is not to be referred to any special region of the ventricles. Kahn and Starkenstein<sup>39</sup> confirm Hering in that they find in *pulsus alternans* produced by glyoxylic acid that the T wave varies considerably in size in the large and small beats, while the R wave is little affected.

The effect on the electrocardiogram of section and stimulation of the extrinsic cardiac nerves has been studied in detail by Rothberger and Winterberg<sup>40</sup>. Increased accelerator influence as a result of vagus section causes increase in P. R is unchanged or smaller and T is much increased. Stimulation of the right stellate ganglion with vagi intact causes a similar change. Stimulation of the left stellate ganglion causes P to become small, R becomes diphasic with pronounced S wave, T usually becomes strongly negative. Increase of vagal effect by section of accelerators causes P and T to undergo marked decrease, while R is increased. They conclude that the effect of increased accelerator influence is the result of a localized strengthening of the contraction, a "partial hyper-systole". In reference to the anatomical distribution of the right and left accelerator fibers they believe that stimulation of the left accelerator

34 Hering Ztschr f exper Pathol u Therap 1909 xii, 363

35 Hering Munchen med Wchnschr, 1908, li, 1417

36 Gaskell Philosoph Tr, 1882, clxxiii 993

37 Trendelenburg Arch f (Anat u) Physiol, 1903, p 271

38 Muskens Jour Physiol, 1907, xxxvi, 104

39 Kahn and Starkenstein Arch f d ges Physiol 1910, cxxxiii 579

40 Rothberger and Winterberg Arch f d ges Physiol 1910 cxxxv, 506

causes negativity of the T wave due to increased strength of contraction of the left ventricle, while increase of the T in a positive direction from stimulation of the right accelerator is due to increased contraction of the right ventricle

The rôle that different parts of the ventricle play in the genesis of the T wave has been studied in an interesting series of experiments by Henle<sup>41</sup> Hering and Biedermann had shown that as a result of the application of a constant electric current to the frog's heart the region of the ventricle under the anode remains uncontracted while the current is passing. If the current is very strong the effect may spread to the entire ventricle, but by using a current of moderate strength a well localized effect may be obtained. For a short time following the cessation of a current which has been passing for some time, the region around the anode contracts more strongly in each systole than the remaining parts of the heart, while the region surrounding the cathode shows diminished activity. These effects likewise involve larger areas the stronger the current employed. If the current is not too strong it is possible to obtain a localized region which contracts to a less or to a greater degree than the remaining ventricular muscle. Henle applied this method to the study of the effects produced by these localized regions of depressed or augmented activity on the electrocardiogram from the heart of frogs and mammals (dogs). Since the passage of a current through the heart would affect the electrocardiogram, he utilized the effects produced on the heart which follow the withdrawal of the current, namely, an augmentation surrounding the anodal and a depression surrounding the cathodal region. One electrode, which can be made either anodal or cathodal, is placed on the heart, the other serves as an indifferent electrode connected with some portion of the body surface. By the use of a commutator a galvanic current is passed through the heart for a period of fifteen to twenty seconds and then by reversal of the key connection is made with the galvanometer and the electrocardiogram obtained from the surface of the heart (base and apex of the ventricle) for the next few beats. With the anode on the base or the cathode on the apex of the heart, the effect on the electrocardiogram in the next few beats following the cessation of the current was an increase in size of the T wave over the normal. The T wave is thus increased in a positive direction when the base contracts stronger or the apex weaker than normal. With the anode on the apex or the cathode on the base the T wave is small, in the first two or three beats following the withdrawal of the current it may be negative. The R wave is practically unaffected. As a result of the current probably the activity of only the superficial layer of the heart muscle is affected, and since this affects only the T wave it is suggested

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41 Henle *Ztschr f Biol*, 1911, 1v, 295

by Henle that the R and T arise from different layers of muscle. The fact that change in the extent of contraction of the musculature at the apex as well as at the base of the ventricle affect the T wave, proves that at the time of occurrence of this wave the apical musculature as well as the basal musculature is in functional activity and that both play a part in its production. This is, of course, opposed to the explanation of the T wave upheld by Gotch and by Kraus and Nicolai.

The production of the T wave, according to the majority of writers, is closely connected with the activity of some special layer or region of ventricular muscle. Only Hoffmann (and perhaps Judin) have suggested that it is representative of contraction of cardiac musculature, irrespective of position. In relation to this conception of great importance is the observation by Straub<sup>42</sup> of the presence of a T wave from the auricle of the isolated frog's heart. After complete cessation of the contraction of the ventricle with continued contraction of the auricles, Straub obtained a diphasic curve followed by a monophasic curve, the latter resembling the T wave of the ventricle. This observation on the frog's heart has been confirmed by Eiger<sup>43</sup> and more recently by Hering<sup>44</sup>. Hering also finds some indication for the presence of a T wave in a curve obtained from the auricles of a dog beating *in situ* after the ventricles have been cut away. He states, however, that such a conclusion can only be arrived at with great reservation and that further work is required to establish an auricular T wave in the electrocardiogram from mammals and from man.

Before closing a review of the recent literature on the electrocardiogram, reference may be made to the interesting series of observations of Paul Hoffmann<sup>45</sup> on the electrocardiogram of the invertebrates. Three types of electrocardiograms, according to this work, are to be recognized. The first type is characterized by a series of oscillations, varying in number from two or three to twenty or more and extending throughout the period of contraction. This type is characteristic of the heart of certain arthropods, namely, *Limulus*, *Mara* and *Astacus*. The heart is evidently in tetanic contraction and the curve is simply a number of action currents rapidly following in succession, each corresponding to an excitation received from the cardiac center in the intrinsic cardiac nervous system. No T wave is present, probably due to the rapidly recurring contractions going to make up the tetanus. The second type of electrocardiogram is characteristic of certain hearts which show a peristaltic contraction, a representative of which is found in the gastropod, *Aplysia*. The electrocardiogram is a simple diphasic curve. Finally

42 Straub Ztschr f Biol, 1910, lxxi, 499

43 Eiger Extr de Bull de l'Acad des Sciences de Cracovia, July, 1911

44 Hering Arch f d ges Physiol, 1912 cxliv 1

45 Hoffmann P. Arch f (Anat u) Physiol, 1911, p 135



the third type is the electrocardiogram characteristic of all the higher animals, found among certain of the higher invertebrates (certain cephalopods) and all the vertebrates. The differences of the electrocardiogram in these different animals are therefore associated with distinct differences in the physiological peculiarities of the heart, and the type of electrocardiogram of the higher animals, including man, is characteristic of the type of activity that is peculiar to the heart of the higher animals.

#### THE RELATION OF THE ELECTROCARDIOGRAM TO OTHER EVENTS IN THE CARDIAC CYCLE

The work of Kahn<sup>15, 16, 17</sup> in this connection has already been referred to. Similar observations have been made by Weiss and Joachim<sup>46</sup> and by Bull.<sup>47</sup> There is general agreement that the R wave precedes by a few hundredths of a second (0.3 to 0.6) the onset of ventricular systole as shown by the rise of intra-ventricular pressure and the first heart sound. The relation of the electrocardiogram to the venous pulse has been studied by Rautenberg.<sup>48</sup> While he agrees that the onset of the R wave precedes the beginning of ventricular systole and finds that the position of the c wave on the venous pulse confirms this view, he concludes that the R wave is nevertheless to be referred to and is representative of the first part of ventricular systole. He assumes that the P wave is to be referred exclusively to contraction of the auricles and its beginning must correspond to the onset of auricular systole. Determining on his curves the distance that the auricular wave of the venous pulse follows the P wave of the electrocardiogram, he applies this correction to the relation between the c wave of the venous pulse (onset of ventricular systole) and the R wave of the electrocardiogram. When this correction is made, he finds that the beginning of the R wave falls in all cases exactly with the beginning of the c wave, and concludes that both represent the same process in the heart, namely, the beginning of ventricular systole. The R wave thus represents the contraction of the ventricular muscles as a whole and not merely of the papillary system, since the contraction of the latter causes no rise in intra-ventricular pressure. The reason that it occurs in point of time before the cardiac muscle contracts is to be referred to the latent period of the heart muscle. Considering for the time that Rautenberg's assumption that the beginning of the P wave is representative in all cases of the onset of auricular systole, and that the correction as applied to the relation between the R and c waves is correct, the work of Kahn<sup>17</sup> on the relation between mechanical movement and electric response which we have already referred to in some detail, is entirely opposed to Rautenberg's interpretation. As will be discussed

46 Weiss and Joachim. *Ztschr. f. klin. Med.*, 1911, LXXIII, 240.

47 Bull. *Quart. Jour. Exper. Physiol.*, 1911, IV, 288.

48 Rautenberg. *Berl. klin. Wchnsch.*, 1910, LXVII, 2190.

later in this paper, we believe we have strong evidence to indicate that the onset of the P wave in by no means all cases corresponds to the onset of auricular systole. The observation of Einthoven<sup>7</sup> and others, that the P-R interval is of different length in different leads to the galvanometer from the same individual, indicates that either the P wave in relation to auricular systole or the R wave in relation to ventricular systole, or both, undergo variation.

We have studied the relation of mechanical systole of the heart to the electrocardiogram, with especial reference to the P-R interval, in man and in the dog. Comparative measurements were made of the a-c interval on the venous pulse and the P-R interval of the electrocardiogram in simultaneous records of the two from fifteen normal men. These show, contrary to the findings of Rautenberg, that the P-R interval on the electrocardiogram does not correspond in the majority of cases with the a-c interval on the venous pulse. Usually the a-c interval is somewhat longer than the P-R interval, so that if P is made coincident with a, c does not fall at the beginning of R, but towards the end of this wave. In a few cases the two intervals are of approximately the same length and in several cycles in these records the a-c interval is definitely shorter than the P-R interval. The probable interpretation of these differences will be discussed later. Our results thus indicate that the P-R interval is not in most cases a measure of the As-Vs interval. The opposite conclusion of Rautenberg seems to have been derived from records which showed a relation other than the usual one. A more interesting point in reference to the interpretation of the electrocardiogram shown by these records is the duration of systole. As is well known, only on certain phlebograms is the end of systole sharply marked by the separation between the t and d waves (Baird<sup>49</sup>). In records from seven of the fifteen individuals the end of systole was evident and these without exception showed that the length of systole, as measured by the c-d interval on the venous pulse, corresponds to an interval on the electrocardiographic curve beginning near or at the end of R to the end of T. If the end of the T wave is representative of termination of the contraction of the ventricular muscle, as is generally recognized to be true, it is evident that the onset of mechanical systole is represented, not by the beginning of the R wave, but by a point at or near the termination of this wave. Figures 1 and 2 are simultaneous records of the jugular pulse and electrocardiogram in man and show the features discussed above. Figure 3 is a record from a dog and gives a comparison of the a-c interval on the jugular pulse and the P-R interval of the electrocardiogram in the same cycle. The venous pulse was recorded by a sound introduced into the right external jugular vein according to the method used by

Fredericq<sup>50</sup> The electrocardiogram in all these records is from Lead II of Einthoven (right anterior and left posterior extremities). In several experiments on dogs we have compared the P-R interval with the As-Vs interval as recorded by suspension curves of the right auricle and right ventricle. These have led to the same conclusion. Certain abnormal conditions of the heart which may cause a wide variation between the two will be discussed later. Finally, in simultaneous records of the venous pulse, electrocardiograms and apex beat in four normal men, the venous pulse has been corrected for transmission by comparison with the cardiographic curve and this correction applied to its relation to the electrocardiogram. When this correction is made, the time from the onset of the P wave to the a wave of the venous pulse is less than the time from the onset of the R wave to the c wave of the venous pulse. If the beginning of P is to be referred to the onset of auricular systole, the beginning of R does not correspond to the onset of ventricular systole. From these observations the following conclusions may be drawn:

- 1 Auricular systole plus auriculo-ventricular conduction time is not accurately represented on the electrocardiogram by the interval from the beginning of the P wave to the beginning of the R wave (P-R interval). In the majority of cases the As-Vs interval corresponds to an interval from the beginning of P to some point on the descending limb of R or the end of this wave.

- 2 The period of systole of the ventricle, or the time from the rise of intraventricular pressure, as marked by the c wave of the venous pulse to the closure of the semilunar valves as marked by the d wave of the venous pulse, is represented in the electrocardiogram by the interval from the end of R to the end of T.

From the work of Keith and Flack,<sup>51</sup> Wybauw,<sup>52</sup> Lewis and Oppenheimer,<sup>53</sup> Brandenburg and Hoffmann,<sup>54</sup> Ganter and Zahn<sup>55</sup> and others, we have strong evidence that the cardiac impulse in the mammalian heart arises in a region of tissue representing embryological remains of the primitive sinus and lying in the adult organ along the sulcus terminalis of the right auricle at its junction with the superior vena cava. The excitation spreads from this region to the auricles and thence to the ventricles by the auriculoventricular bundle. The question at once arises whether or not the activity of the so-called sinus region is represented in the electrocardiogram. Is the P wave representative entirely of activity of the auricles, or does the cardiac impulse before reaching the

50 Fredericq *Arch internat de physiol*, 1907, v, 1

51 Keith and Flack *Jour Anat and Physiol*, 1907, xli, 172

52 Wybauw *Arch internat de Physiol*, 1910, x, 78

53 Lewis, Oppenheimer and Oppenheimer *Heart*, 1911, ii, 147

54 Brandenburg and Hoffmann *Med Klin*, 1912, viii, 16

55 Ganter and Zahn *Zentralbl f Physiol*, 1912, xxv, 782

auricular tissue proper play a part in the production of the electrocardiographic curve? We have recently studied in a series of experiments on the dog's heart *in situ* the conduction of the excitation from the sinus region, the results from which will form the subject of another paper, but certain facts bearing on the present problem may be discussed here. The Keith-Flack node manifests development of a negative potential in the dog's heart from 0.025 to 0.03 second before the body of the right auricle. This result was obtained by measuring the time from the occurrence of negativity in these two regions in relation to mechanical systole of the auricle. One electrode was placed on the node, another on the auricle and these connected in turn through the galvanometer to an indifferent electrode on the left hind leg of the animal, the systole of the right auricle being recorded at the same time by suspension. There is, therefore, a slight delay in the passage of the impulse from the node to the auricle, a sino-auricular interval which amounts, under normal conditions, to from  $1/5$  to  $1/3$  the auriculoventricular interval in the same animal. By comparing in the same experiments the relation of the onset of the P wave of the electrocardiogram to mechanical systole of the auricle, it was possible to determine whether the negativity in the sinus region formed the first part of the P wave or whether the wave is to be referred exclusively to excitation in the auricle. An example will make this clear. In one experiment an electrode placed on the sinus region and connected with an indifferent electrode on the left hind leg, showed that the first negativity developed at the sinus preceded the onset of mechanical systole of the auricle by 0.08 second. The lower part of the body of the right auricle developed negativity 0.05 second before auricular systole. The P wave of the electrocardiogram (leads from right anterior and left posterior extremities) finally began 0.07 second before auricular systole. The first two of these determinations were made in the same record by means of a key used to connect the electrodes on the sinus and auricle in turn with the galvanometer and indifferent electrode. The relation of the P wave to auricular systole was determined from a record immediately following the proceeding. It is evident from the data in this experiment that the wave of negativity passed from the sinus node to the body of the auricle within 0.03 second and that the P wave of the electrocardiogram was in part made up of this negativity, while still in the sinus region and in part after it had spread to the auricles. Our experiments have also demonstrated that there is no restricted path of tissue by which the impulse spreads from the sinus to the auricle. Such conduction occurs by diffuse paths, and this is probably the explanation as to why the manifestation of sinus activity and of auricular activity on the electrocardiogram are fused to form a single wave (P), and do not form two separate waves. A splitting of the P wave has been described by Heering<sup>6</sup> and others. Heering suggested that

the first part represented activity of the sinus the second part activity of the auricles. We have seen a similar division into two waves in an experiment in which the sinus region was partially isolated from the auricle by cuts through the cardiac tissue and this suggests that a splitting of the P wave may indicate unusual difficulty in conduction from the sinus node to the auricle. The point we wish to emphasize here however is that the P wave of the electrocardiogram in the majority of cases at least is a composite of the spread of the excitation in the sinus region and in the auricles. The onset of this wave does not, as a rule, correspond to the development of activity in the auricles but is coincident with or more frequently begins a short time after the excitation becomes evident in the sinus region. No separate wave occurs normally in the electrocardiogram of mammals indicating activity of the sinus because the region is connected with the auricles by many and diffuse paths and there is a relatively small delay in the passage of the excitation to the auricle. In the cold-blooded heart the sinus, although present as a separate chamber, the contraction of which is separated by a considerable interval from that of the auricles, does not as a rule produce any effect in the electrocardiogram, probably because its activity is too small. Using a very sensitive thread in the galvanometer we have obtained evidence of a wave preceding the P wave of the electrocardiogram in the tortoise from leads from the body tissues of the animals and perfectly clear and definite results when the leads were from the exposed heart, one from the sinus the other from the ventricle. An example is given in Figure 1. There is a wave resulting from a sinus activity, followed by the usual P, R and T waves. That leads from the surface of the mammalian heart fail to show under normal conditions any evidence of a sinus wave separate from that of the wave produced by activity in the auricle would seem then to be the essential difference between the electrocardiogram of the cold-blooded heart and the mammalian heart and to be the expression of the difference in the two cases of the physiological relation between the sinus and auricles. In the example given above, the data are such as to lead to the conclusion that the first onset of negativity in the sinus region does not give rise to the P wave. In the majority of cases this is true, and while only in exceptional cases does the P wave begin first when the activity reaches the auricle, usually the very first development of negativity in the sinus does not affect the electrocardiogram. Probably if the galvanometer in all cases were sufficiently delicate, the onset of the P wave would correspond always to initial negativity of the sinus.

Having thus to consider the P wave as made up in practically all cases in part by activity in the sinus region, and the extent to which this enters varying in different cases we have at once an evident factor to account, in part at least, for differences between the P-R interval and the

interval from auricular systole to ventricular systole (As-Vs interval), as measured by mechanical means. If one explains the electrocardiogram on the hypothesis that it represents two separate processes occurring in the heart muscle during its activity, namely, conduction of the excitation and contraction of the muscle, the P and R wave are to be regarded as representing the former process in the auricles and ventricles, respectively. If the P and R waves are then not manifestations of contraction of the auricular and ventricular muscle, but of the spread of the wave of excitation, another factor may be considered which may act to change the P-R interval independently of the As-Vs interval. It is conceivable that the period from the time of entrance of the excitation into the muscle to the contraction may undergo variations and may be different in the case of the auricle and ventricle. The latent period of mammalian heart muscle to direct stimulation varies markedly at different times in the cardiac cycle (Hirschfelder and Eyster<sup>56</sup>). A third factor which may perhaps alter the P-R interval without changing the As-Vs interval is variation in the conductivity from the sinus region to the auricle. By application of nicotine to the sinus and basal portions of the right auricle we have found that the P-R interval may become actually twice as long as the As-Vs interval, as measured by suspension of the right auricle and right ventricle. The change in the P-R interval in this case was shown to be due entirely to an earlier occurrence of the P wave before mechanical auricular systole. An example of these experiments may be given. Before application of the nicotine the P-R interval averaged 0.10 second, the As-Vs interval 0.13 second. These were measured from the same cycles. The P wave preceded auricular systole by 0.055 second. Following the application of 50 per cent nicotine the P-R interval averaged 0.13 second, the As-Vs interval 0.06 second, P preceded auricular systole 0.13 second.

Whether these may or may not be the main factors involved in causing variations in the P-R interval independently of the As-Vs interval the fact is evident that it can be shown experimentally that the P-R interval is not an accurate measure for this period, and that the two may show independent variation. As we have seen, usually the P-R interval is a few hundredths of a second shorter than the As-Vs period. The occurrence of the P wave before the excitation enters the auricle would tend to make it larger, yet normally the reverse is true. While perhaps a definite answer cannot be given as to the cause of this it seems to us that it may be well explained on the following grounds. When the excitation reaches the auricle it affects at once muscles the contraction of which cause decrease in the internal capacity of this chamber. This is not true in the case of the ventricle. The excitation

<sup>56</sup> Hirschfelder and Eyster, *Am Jour Physiol*, 1907, xviii, 222.

passes down the His bundle into the papillary system and is thence distributed to the remainder of the ventricular musculature. It is not until the circular fibers of the ventricle are in activity that any decrease in the interval capacity of the ventricle occurs and a rise of intra-ventricular pressure results. The work of Hering<sup>10</sup> has demonstrated that the papillary muscles contract at least 0.2 to 0.3 second before the main mass of ventricular muscle.

The fact that the length of systole is expressed on the electrocardiogram, not by the distance from the beginning of R, but from the end of R to the end of T, would seem again to point to the conclusion that the R wave can have nothing to do with the contraction of any musculature which tends to decrease the size of the ventricle. In strong support of this is the experimental proof of Kahn,<sup>17</sup> to which we have previously referred, that the muscle which, by its activity, produces the R wave must contract following this wave a much shorter period of time than does the mechanical systole of the ventricle.

#### THE RELATION OF THE LINE OF ISOPOTENTIAL TO THE FORMATION OF THE ELECTROCARDIOGRAM

As has been pointed out, particularly by Kraus and Nicolai,<sup>3</sup> the electrocardiogram is the expression of the algebraic sum of many electric potential differences conducted away from the heart by its interior and exterior surfaces to the peripheral tissues. The whole heart serves as an indifferent conductor for potential differences arising at any point within the organ and the actual potential at any given point at any time is due to the activity in this region modified by activity occurring at this time in all other regions. We may suppose to exist, as was first described by Waller,<sup>1</sup> in reference to any two leads from the extremities, a line or equator of equipotential passing through the heart between base and apex. A preponderance of negative potential above this line (basal portions of heart) causes the movement of the galvanometer connected with the two hands in such a way as to indicate relative negativity of the electrode connected with the right hand. In leads from a hand and foot, the hand assumes this relative negativity. A preponderance of negativity below this line causes movement of the galvanometer in the opposite direction.

We have attempted to afford experimental evidence for this assumption by artificially producing a condition of negativity in various regions of the heart and determining the effect produced on the galvanometer connected in the usual way with two leads from the extremities. Dead dogs were used. The animal was placed in a large sheet-iron tank, the bottom of which was covered with saline solution to a depth of several centimeters. Leads to the galvanometer were made from the right

anterior and left posterior extremities. Six non-polarizable electrodes were placed on various regions of the heart. These were connected with a switch with six contact points by means of which any one of the electrodes could be placed in a circuit with a battery and a large sheet-iron plate on the bottom of the tank containing the animal. By this means a current could be sent through the animal, entering by a large area through the skin of the back and leaving by a much smaller area on the surface of the heart. While this condition probably resembles little the actual condition present in the beating heart in which a potential difference arises between two points from activity of the muscle, we were able to demonstrate the fact that a difference of potential arising under the conditions of our experiment affect the galvanometer connected with the two limbs differently, depending on what region of the heart shows this change in potential. The relation between different points on the heart may thus be compared and a line of isopotential demonstrated under the conditions present. Change in potential along this line causes no movement of the galvanometer. A negative charge above this line causes the galvanometer to move in a direction indicating relative negativity of the electrode connected with the anterior limb. A negative charge below this line causes the galvanometer to move in the opposite direction. The actual position of the line of equipotential in our experiments was an arbitrary one and could be shifted by varying the position and extent of contact of the animal with the salt solution in the tank. The relation of other parts of the heart to the region transversed by this line, however, remained quite constant. The position of the six electrodes was as follows:

- 1 (a) Region of the sinus (Keith-Flack) node, (b) on body of right auricle
- 2 Region of the auriculoventricular (Tawara) node at the base of the interauricular septum
- 3 Auriculoventricular bundle near bifurcation
- 4 Left ventricular apex
- 5 Right ventricular base
- 6 Aortic base of left ventricle

The results from the three experiments of this character may be summarized as follows: When the line of isopotential passed along the region of the ventricles, a movement of the galvanometer indicating negativity of the anterior electrode (right fore limb) occurred when the current was passed through the electrodes on the sinus, the right auricle, the A-V bundle and the region of the Tawara nodes. The extent of movement was in the order named. The two ventricular bases showed movement in the same direction as the above and to about an equal degree. No marked difference was obtained, but in two of the three



experiments the movement was slightly greater for the aortic base than for the base of the right ventricle. Measurements from a record may be given as follows:

Sinus	—13
Intraventricular septum	—12
A-V bundle	—10
Left ventricular apex	+ 1
Right ventricular base	—10
Aortic base of left ventricle	—10

The figures refer to the movement of the thread in millimeters. The minus sign indicates movement showing relative negativity of the anterior electrode. The plus sign indicates negativity of the posterior electrode. By shifting the contact of the back of the animal with the salt solution in this experiment, a movement of the thread indicating relative negativity of the anterior electrode occurred in all cases. The relation between the extent of movement in each case remained however without change.

While we realize that the application of any results drawn from the above experiments to the normal electrocardiogram must be applied with all due reservation, we believe the fact that the basal regions of the ventricle show similar relations to the leads from the limbs as do the supraventricular regions of the heart and particularly the absence of any marked difference between the base of the right and left ventricles, is at least suggestive. It would seem to be opposed to the views of Einthoven<sup>2</sup> and Selenin<sup>3</sup> that the two ventricles in their activity represent the opposing influences in the production of the normal electrocardiogram and would tend to lay stress on the difference between base and apex in this connection. The fact that a line of isopotential can be obtained experimentally under the conditions described and that there is general agreement in the curves obtained with those representing potential changes in the normal beating heart as for example, the fact that activity of the right auricle produces always in the beating heart relative negativity of the anterior electrode while activity of the ventricular apex affects movement in the electrocardiogram in the opposite direction seem to us to offer support to the view that normally there is such a region of isopotential between base and apex and it is the balance of potential on the two sides of this which determines whether the electrocardiographic curve moves in one direction or the other. The simplest explanation of why the P wave, for example, is monophasic in the electrocardiogram from the extremities while it may be diphasic in direct leads from the auricle, is that all of the activity producing it is above the line of isopotential. Whether or not the T wave is positive or negative in direction may also be well explained by the resultant of activity above and below this line. In a T wave directed in the same

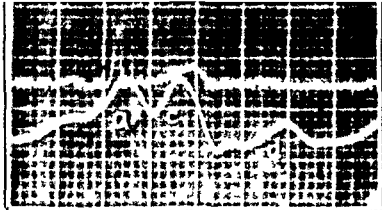


Fig 1

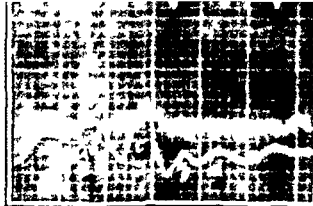


Fig 2



Fig 3

Fig 1—Electrocardiogram (Lead II) and venous pulse from man Time record in 1/5 sec To show comparative lengths of the P R and a c intervals and the R T and e d intervals

Fig 2—Similar to Figure 1

Fig 3—Electrocardiogram (Lead II) and venous pulse from a dog to compare the length of the P R and a c intervals

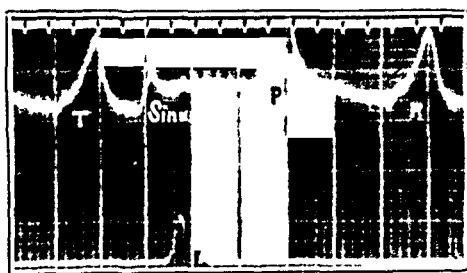


Fig 4

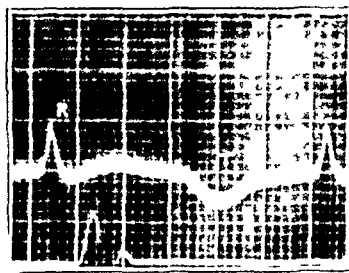


Fig 5

Fig 4—Electrocardiogram from superficial leads from the exposed tortoise heart to show the wave arising from sinus activity The leads to the galvanometer were from the sinus and ventricular apex The lowest line signals the mechanical systole of the sinus The electrocardiographic record shows a sinus wave followed by a P and R wave The time record is in 1/5 second

Fig 5—Electrocardiographic curve obtained from the exposed tortoise heart (leads from right auricle and ventricular apex) in which the ventricle had ceased beating as a result of the application of a second Stimulus ligature Time in 1/5 sec intervals The lowest line signals the auricular systole

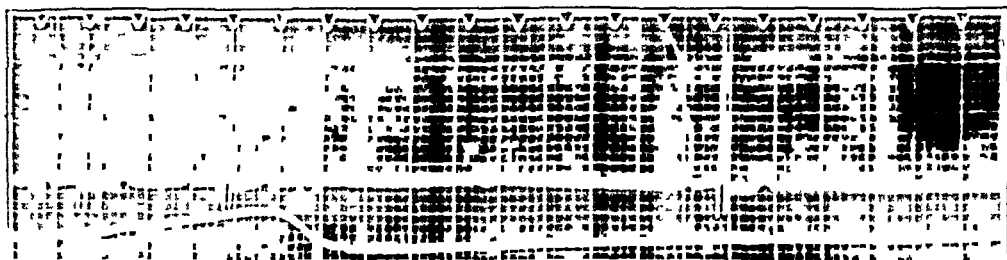


Fig 6

Fig 6—Electrocardiogram (Lead II) from a dog showing heart block as a result of a toxic dose of morphin The blocked cycles show a small wave following the P which is interpreted as an auricular J wave

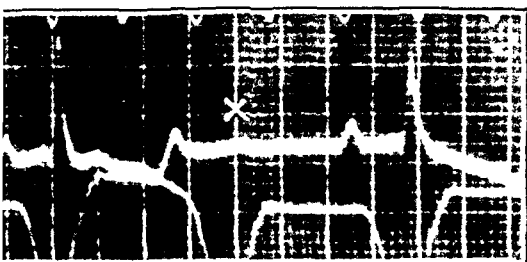


Fig 7

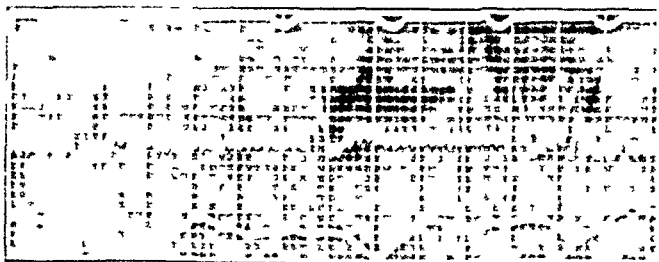


Fig 8

Fig 7—Electrocardiogram (Lead II) from a dog showing heart block as a result of pressure applied to the region of the auriculoventricular node The blocked cycle shows an auricular J The lowest line records the mechanical systole of the right auricle

Fig 8—Curve from dog's heart *in situ* with leads to the galvanometer from the exposed right auricle and from the left posterior leg Heart block from vagus stimulation showing the auricular J The lowest line records the mechanical systole of the right auricle

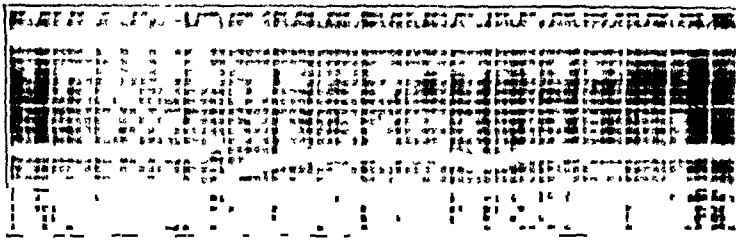


Fig 9—Action current from a longitudinal strip of ventricular muscle from the tortoise ventricle not including any of the region of the aortic base. Shows a biphasic R followed by a T wave accompanying the contraction resulting from mechanical stimulation. The lowest line records the contraction.

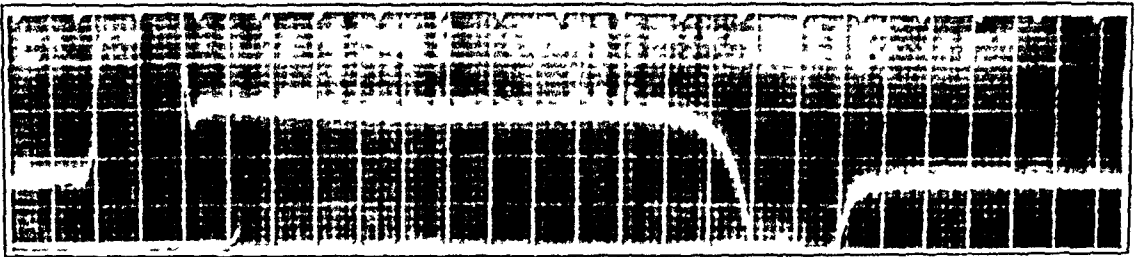


Fig 10—Action current from a strip of ventricular muscle cut from the apical region of the tortoise ventricle. Monophasic R followed by T. The lowest line signals the contraction of the strip.



Fig 11—Similar to Figure 10. T in same direction as first movement of R.



Fig 12—Action current from strip cut crosswise from the mid-region of a tortoise ventricle and stimulated mechanically. The contraction of the strip is signaled by the lowest line of the record.



Fig 13—Action current from the ventricle of a cat after removal of the basal regions. Mechanical stimulation. The lowest line of the record shows the duration of contraction.

Fig 14—Showing the effect on the T wave of the auricle of vagus stimulation. Leads from right auricle and basal part of quiescent ventricle. The period of vagus stimulation is indicated by the small rapid oscillations of the galvanometer thread produced by the escape of the stimulating current. The lowest line records the mechanical systole.

Fig 15—Similar to Figure 14. Tortoise heart, ventricle quiescent as a result of a second Stannius ligature.

Fig 16—Similar to preceding. Shows the transition stages of the results of vagus stimulation. The mechanical systole of the auricle is signaled by the lowest line.

Fig 17—Similar to preceding. Shows the transition stages of the results of vagus stimulation. The record was stopped for a short period in order to obtain recovery stages following the stimulation. The mechanical systole of the auricle is signaled by the lowest line.

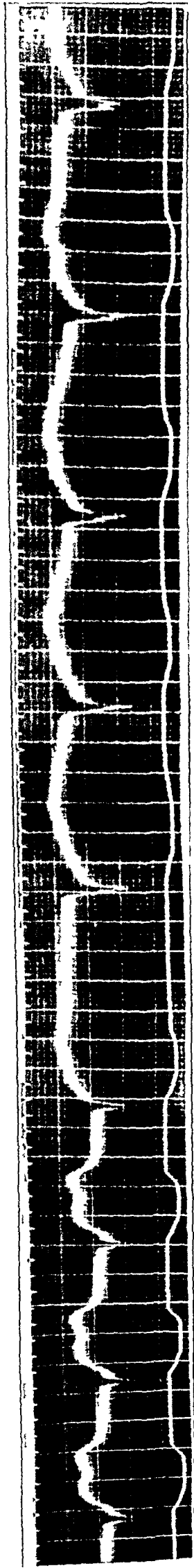


Fig 17—Action current from auricle of tortoise heart with quiescent ventricle in similar preparation to those of the preceding figures Shows the effect on the auricular T wave of the application of Ringer's fluid at 4 C The lowest line records the mechanical systole of the auricle

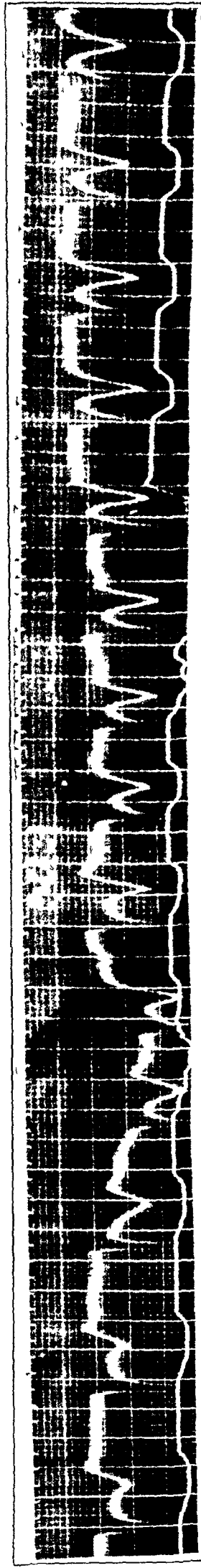


Fig 18—Similar preparation to preceding, showing the result of the application of Ringer's fluid at 12 C to the heart

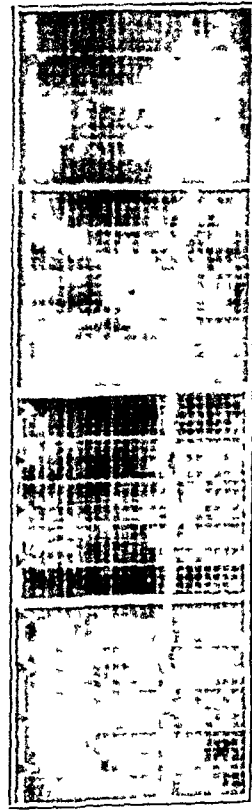


Fig 19—Four electrocardiograms from the same individual taken over a short space of time with thread of different sensitivity Lead II

direction as the P, the predominant activity producing it would be in the ventricular bases, while a T in the opposite direction (so-called negative T wave) would seem to depend on excess of activity in the more apically lying ventricular musculature.

#### THE INTERPRETATION OF THE T WAVE

The various views that have been advanced to explain the T wave have been described. Our own observations support the view of Hoffmann,<sup>23</sup> in so far as this investigator separates between conduction and contraction in cardiac muscle and refers the T wave to the latter.

We have succeeded in demonstrating the presence of a wave resembling in all characteristics the T wave of the electrocardiogram in (1) the auricle of the cold-blooded heart, (2) the auricle of the mammalian heart, (3) the ventricle of the tortoise's heart after destruction of the musculature around the aortic ring, (4) in simple strips from the tortoise's ventricle, from the apical as well as the basal regions, and (5) from strips cut from the mammalian ventricle. When isolated, and changes in other regions prevented from modifying the curve obtained, all of these show as the result of stimulation and a sufficiently sensitive galvanometer two sharply marked electrical changes—first, a rapid monophasic or diphasic curve, followed by a much slower and more prolonged variation. Figure 5 shows the curve obtained from a tortoise's heart with a second Stannius ligature and quiescent ventricle. The heart was *in situ* and the leads to the galvanometer from the right auricle and ventricle. Each auricular beat shows a rapid electrical change followed by a much slower variation in the opposite direction. The time of auricular contraction is marked by a signal (lowest curve of record). In this particular case the second wave is opposite in direction to the first and might be considered as the second part of a diphasic variation. Opposed to this interpretation is the great delay between the two movements, the fact that the first wave resembles an R, the second a T wave and that frequently the two movements are in the same direction, or the first may be clearly diphasic and thus be followed after a time by a slower monophasic change. Figure 6 shows a T wave of the auricle of a dog in partial auriculoventricular block resulting from a toxic dose of morphin.<sup>24</sup> The electrocardiogram was obtained in the usual way from the right anterior and left posterior extremities. Following the P wave of the blocked cycle there is a small but definite prolonged variation in the same direction. Figure 7 shows a small T wave in the auricle in partial auriculoventricular block in the dog's heart arising from pressure on the region of the auriculoventricular node. The position of the auricular T is marked by an X. The lowest line of this record is a

<sup>23</sup> Fester and Meck. *Heart* 1912, iv, 59.

suspension curve of the right auricle, the downstroke representing systole. The heart was *in situ*, the chest opened and the leads to the galvanometer from the right anterior and left posterior extremities. This wave occurred regularly in all cycles where the conduction was blocked. It is evident in the unblocked cycles that the development of this wave would be impossible, since it would be entirely obscured by the ventricular R wave. Figure 8 is a curve obtained from a dog with heart *in situ* and leads from exposed right auricle and left posterior leg. As a result of stimulation of the vagus the first two cycles show only auricular contractions. The lowest line of the record records these contractions. Each beat of the auricle causes a rapid diphasic curve followed by a slow monophasic curve. In the third cycle the auricular contraction is followed by a systole of the ventricle and a diphasic ventricular curve obscures the formation of the auricular T wave.<sup>58</sup> Pronounced T waves have been obtained from the tortoise's ventricle after complete destruction of the aortic regions and from strips of ventricular muscle cut from various regions of the ventricle. Figure 9 is a curve obtained from a longitudinal strip of ventricular muscle not including any of the region of the aortic base. Mechanical stimulation of one end of the strip resulted in a contraction with the production of a diphasic curve followed after a considerable interval by a slow monophasic curve. Figure 10 is a curve from a strip cut from the apex of a tortoise's ventricle and stimulated mechanically. The galvanometer was very sensitive and shows movements that carried the shadow off the record. There is a monophasic curve followed after a pause of over one and a half seconds by another large monophasic change in the opposite direction. Figure 11 is from a similar strip and shows a rapid mono- or partially diphasic curve with a slower change in the same direction as the original movement of the galvanometer thread. Figure 12 is a curve from a strip cut crosswise from the mid-region of a tortoise's ventricle and stimulated mechanically. There is an initial electrical change followed by a slower movement in the same direction.

To explain satisfactorily these curves as a result of contraction alone would seem to be impossible. In Figure 12, for example, it would be necessary on such an assumption to suppose that the contraction began at the end stimulated and spread out from this region, and that after a relatively long period of time there occurred a second contraction following the same course. If one assumes, however, that the two electrical waves actually represent two different processes, conduction of the excitation and contraction of the muscle, the second following the first after a certain interval, the interpretation is not difficult.

<sup>58</sup> Fig 13, Plate 17 of Samojloff's paper<sup>19</sup> shows a well developed auricular T wave in auriculoventricular block from vagus stimulation. The author makes no reference to this in the text.

Figure 13 is a curve obtained from mechanical stimulation of the ventricle of a cat, removed from the body and suspended. The auricles and whole basal region of the ventricle, including the region of the origin of the aorta and pulmonary artery, were cut away. The lowest line of the record records the contraction. It will be seen that this begins after the first electrical wave is completed and ends coincidently with the termination of the second electrical wave. The relation of the contraction to the two waves is strikingly like the relation of the R and T waves of the normal electrocardiogram to mechanical systole of the ventricles as discussed in a preceding section of this paper.

That we are actually dealing, in all cases considered above, with a wave similar in all essential details to the T wave of the electrocardiogram is indicated on several grounds. In the first place it is difficult or impossible to interpret the curves in any other way. In the second place, the wave which we believe to be the T wave in the ventricular strips shows a peculiarity in reference to its form which was first noted by Einthoven as characteristic of the T wave of the electrocardiogram. The T wave is characterized by a slow rise and a relatively rapid fall and in this is unique among physiological curves. Finally, we have performed a series of experiments on the supposed auricular T wave of the tortoise's heart which show it to undergo variations in size and direction under certain experimental conditions which have been shown to be characteristic of the T wave of the electrocardiogram of the ventricle. These include the effect of vagus stimulation and of heat and cold applied directly to the heart. Samojloff<sup>19</sup> has analyzed the influence of vagus stimulation on the electrocardiogram of the frog's heart as follows. During vagus stimulation the T wave of the ventricle shows a decrease in the upward direction (when the leads are such that R is positive in direction), or changes from a positive to a negative T. The R wave is not affected, but the R-T interval is shortened. Following the stimulation the T gradually returns to its normal direction and size and the R-T interval becomes normal. During the vagus stimulation the T does not change in direction abruptly as a rule, but the first effect is usually that along with the decrease of the T, a movement in the opposite direction begins preceding the original purely positive wave. At this time the T is really diphasic with the first movement in the opposite direction to the original wave. Finally, the last part of the diphasic curve disappears and the T is represented by a monophasic curve in the opposite direction to the original wave. This also explains why the R-T interval is shortened. The reverse process occurs during the return to normal after the stimulation.

Figure 14 shows that similar changes occur in the T wave of the auricle as a result of vagus stimulation as described by Samojloff for the T wave of the ventricle. The record is from a tortoise's heart in



which the ventricle is quiescent as a result of a second Stannius ligature. The leads to the galvanometer were from the right auricle and basal part of the quiescent ventricle and are connected in such a way that the P wave (which for convenience of description may be designated here as the "R" wave of the auricle) is directed downward. The lowest line is the contraction curve of the auricle recorded by suspension. It is evident here, as in previous records, that the contraction begins after the "R" is completed and ends near the end of T. Stimulation of the right vagus was begun toward the end of the second cycle shown on the record, and its duration is indicated by the small oscillations it produces in the thread of the galvanometer. The first two cycles are before vagus stimulation and show an auricular T wave in the same direction as the P (auricular "R"). In the third cycle the T has already begun to manifest change in direction as a result of vagus stimulation, while the "R" wave is unchanged. In the fourth cycle the change is complete. Following the stimulation the first few beats show a still further development of this change with a marked shortening of the R-T interval. The condition tends to pass off toward the end of the record. Figure 15 shows a similar result to a less marked degree. The conditions here were the same as in the preceding experiment. The "R" wave is diphasic. The T wave before stimulation is a long slow change opposite in direction to the initial change of the "R". Vagus stimulation, the onset and duration of which is shown by the effect on the thread, decreases the T wave slightly in height and apparently splits it into two parts. The "R" is unchanged. Figure 16 shows the transition stages in the change of the auricular T wave as described by Samojloff for the ventricular T. The conditions were the same as in preceding experiments. Before stimulation, the T wave is directed downward and is a long slow wave resembling the T of Figure 15. The recording apparatus was stopped for a short time following the vagus stimulation and during the recovery a diphasic T wave with the initial change in the opposite direction to the original T is apparent. The onset of auricular systole in this record is marked by a signal.

Straub<sup>20</sup> has shown that in the frog warming the heart increased the size of the T wave of the ventricle while cooling the ventricle causes the T wave to become small or negative. We have found that the T wave of the auricle of the tortoise behaves similarly. Figure 17 shows the effect of application of cold Ringer's fluid (4 C.) to the exposed heart of the tortoise. The ventricle was quiescent as a result of a second Stannius ligature. The leads to the galvanometer were from the right auricle near the tip and the base of the quiescent ventricle. The cold saline solution was applied after the third cycle. The effect is a practically complete abolition of the T wave of the auricle. The P wave is also reduced and shows division. Figure 18 is from a similar preparation.

and shows the effect of application of Ringer's solution at 42 C. The T wave increases in size from 10 to 20 millimeters. The effect in each case passed off shortly after the records shown and the condition returned to normal.

In a recent paper,<sup>59</sup> in which we have attempted to trace experimentally the course of the excitation over the tortoise heart, we have given a number of facts which we believe incompatible with Gotch's interpretation of the T wave. The excitation in its spread over the heart was traced by means of the action current recorded by leads from various points on the surface of the heart. The experiments are fully described in this paper and only certain points will be referred to here. In leads to the galvanometer from the aortic base and apex of the ventricle, the negativity in the former preceded in all of eighteen experiments. In eleven of these the T wave was in the same direction as the initial movement of the R wave, in seven it was in the opposite direction. It is difficult to understand on Gotch's view how the T wave can ever be opposite to the R in this lead, since such a feature would imply, on his interpretation, terminal activity of the apex. In the experiments of this series eighteen different leads from various regions of the heart were compared. In twelve of these leads the results were uniform in a great majority of the experiments as to the direction of the initial movement in the R wave. In some of these cases the R was monophasic, in others diphasic, and this was true not only in different leads in the same heart, but the same lead in different hearts. Marked variability was present, however, in the direction of the T wave. The variations in one lead, the aortic base and apex, are given above. While in most leads there was a distinct majority of cases in which the T wave had a certain direction in relation to the direction of the R, and thus a more or less typical curve for any given lead, exceptions were always present and in some cases the T was in the opposite or in the same direction as the R in about an equal number of cases. Certain other examples of this besides the aortic base-apex lead may be given. In eighteen left anterior base and apex leads the R wave in all cases was in a direction indicating primary negativity of the base. The T wave was in the same direction in twelve cases, in the opposite direction in six. In the lead from the left and right posterior ventricular bases, the former showed initial negativity in eighteen of twenty-three cases. In these eighteen cases the T was in the same direction in ten cases, in the opposite direction in eight. Many other examples could be given, but these are sufficient to illustrate the fact that the T wave in the same leads from the heart may vary in direction in reference to the R to a marked degree. Two hearts which show in the various leads exactly the same sequence of activity in the

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59 Meek and Eyster. *Am Jour Physiol*, 1912, **XXI**, 31

different regions, as indicated by the direction of the R waves, may thus have T waves in the opposite direction. If the T wave as well as the R is to be referred to conduction of the excitation we should have to assume, therefore, marked differences in the spread of the excitation in these two cases. In each case the initial course of the impulse as shown by the same direction of the R waves is the same, but if the T wave is involved in the interpretation the final course of the impulse would be exactly opposite. That the initial course should be so constant, while the terminal course shows such marked variations, would seem very improbable. A much more satisfactory explanation, and one more in accord with other known facts, is to assume that the R and T waves represent different phenomena. The former we believe to be representatives of the spread of the excitation, the latter of the active contraction of the muscle. Since the spread of the excitation in the normal heart is probably a constant factor, the R wave in the same leads from different hearts is practically constant in direction. The direction that the T wave assumes in relation to the R is probably determined by the region of the ventricle that manifests the greatest activity in the contraction or that remains contracted for the longest time. Many known experimental influences may modify the extent of contraction in different regions of the ventricle and such modifications probably occur as a result of the action of various uncontrolled factors in many experiments, particularly when the heart is exposed. Whether this be the true explanation or not, the facts stated offer other examples of variations in the direction and character of the T wave with unchanged R wave and offer additional support to the view that these two waves represent essentially different activities in the heart.

The R wave with leads from two points on the exposed heart, or from two ends of a strip of cardiac muscle may be either monophasic or diphasic. The same lead in two hearts may give a monophasic R in one case and a diphasic R in the other. The curve obtained in the passage of an excitation over a muscle between two electrodes is usually diphasic, but as is well known, monophasic curves are not infrequent. The apparent explanation in the latter case is that the activity associated with the excitation, while spreading to the second electrode, remains preponderant at the region of the first electrode.

A further point may be noted in reference to our experiments on the exposed heart of the tortoise, namely that the size of the T wave is usually greatest when one or both of the electrodes were on a part of the heart which enters into strong contraction. The smallest T waves were obtained from leads from the auriculoventricular ring where contraction is very small.

We shall not attempt to give in this paper a review of the rather large literature concerned with the question as to whether conduction and contraction are to be regarded as different phenomena in skeletal muscle. The studies of v Brücke<sup>60</sup> and Noyons,<sup>61</sup> concerning the action of asphyxia on the relation between the action current and extent of contraction would seem to show that the two may vary independently. The mere fact that a nerve manifests conduction and no contraction would suggest the possibility of the independence of the two processes in muscle. The experiments of Hoffmann on the heart in which contraction was abolished by drugs and the R wave unaffected, have been referred to in detail. Trendelenburg,<sup>62</sup> in a recent study of the relation between the refractory phase of the heart and the action current, finds that one may be made to vary independently of the other. He finds also in standstill from muscarin, that the action current of the heart may be very little affected.

The normal electrocardiogram is usually described as showing a level phase between the end of the R and the onset of the T wave, explained, as we have seen, by most writers as due to simultaneous contraction of the whole musculature of the ventricle and the numerous action currents arising neutralizing one another so as to give no demonstrable difference in potential. This explanation has been objected to by certain writers (Rautenberg, Rehfish) on the theoretical ground that such a perfect antagonism could not be expected in all cases. We have become convinced by a study of our electrocardiographic curves, as well as those published by others, that the normal electrocardiogram is not characterized by a period of equal potential between base and apex at this time. In the great majority of records, especially when the galvanometer is somewhat more sensitive than that ordinarily used in recording electrocardiograms from man, the curve shows a gradual rise following the end of R (or S). When the T is well developed the curve may proceed upward at once on the completion of the R without any evidence whatever of a horizontal period. Records obtained from the same individual with successive increase in the sensitiveness of the galvanometer, show that the apparently horizontal portion of the electrocardiogram disappears with increase in delicacy (Fig 19). The condition, therefore, which gives rise to the T wave is actually present very soon after the termination of the R wave. It may reach its full development rapidly and the crest of T be reached without interruption, or at first it may be present in relatively small degree and develop more rapidly toward the end of systole.

60 v Brücke *Arch f d ges Physiol*, 1908, cxliv, 215

61 Noyons *Onderzoek physiol Lab Utrecht v Ruks*, 1909, x, 215

62 Trendelenburg *Arch f die ges Physiol*, 1912, cxliv, 39

## THE INTERPRETATION OF THE NORMAL ELECTROCARDIOGRAM

Our own experiments and a review of the literature has led us to agree essentially with the interpretation of Hoffmann, that the normal electrocardiogram is the expression of two different processes occurring in the heart muscle during its activity namely the spread of the excitation and the mechanical shortening of the muscle. The facts which speak for such a view may be stated briefly. In the nerve where conduction alone is present, a single monophasic or diphasic electric response is obtained. In skeletal muscle this rapid electrical change is followed by a slower and more prolonged monophasic variation. These two electrical manifestations, present also in cardiac muscle from all parts of the ventricle as well as from the auricle, may vary independently, one may be abolished and the other persist, or either may change in size independently of the other.

The electrocardiogram as obtained in the usual way with leads from the extremities is an expression of those two processes. In the usual electrocardiogram there is no electrical expression of the contraction of the auricle, while the electrical expression of the ventricular contraction is evident (T wave). This is due to the fact that the ventricle contracts much more strongly, but especially that the electric wave resulting from this contraction is not obscured by any process of conduction occurring at this time. The auricles during their contraction as well as the ventricle develop electrical energy but the movement of the galvanometer that is produced is ordinarily obscured by the wave (R) associated with conduction of the excitation in the ventricle. When such conduction is prevented (auriculoventricular heart block isolated auricles), the contraction of the auricles causes a definite electrical change (T wave of the auricle) to be evident on the electrocardiogram.

The P wave of the electrocardiogram is to be referred to passage of the excitation from the point of origin in the sinus region over the auricle. In the cold-blooded heart where the activity of the sinus and of the auricle are separated by a relatively long interval, the P wave is preceded, when the galvanometer is sufficiently sensitive, by a wave representing the passage of the excitation over the sinus. In the mammalian heart, on the other hand, where the sinus is closely incorporated with the right auricle while its activity precedes that of the auricle by only a very short period (.03 second), even with the most sensitive galvanometer no evidence is obtained of a separate activity preceding the P wave. There may be, however, a division of the P wave when the conduction is delayed between the sinus and auricle and the conditions approach that present in the cold-blooded heart. Under normal conditions in the mammalian heart, however, the P wave is due in part to sinus activity, as is shown by comparative measurement between the onset of sinus activity and auricular contraction, on the one hand, and

of the P wave and auricular contraction on the other hand. Whether or not the passage of the impulse through the auriculoventricular conductive system, the His bundle and its main branches to the right and left ventricle enters into the formation of the R wave, is not clear from our present knowledge. Against this is the presence of an R wave in the cold-blooded heart, where the auriculoventricular conduction system is less specialized and in conduction between any parts of the ventricle or over a strip of heart muscle. It is also extremely difficult to explain the Q wave on this assumption. While this wave may perhaps not be a feature of the strictly normal electrocardiogram, it is present in many cases, and must be explained when present. Hoffmann does not commit himself to the exact portion of the conducting system which is responsible for the R wave. Nicolai has attempted to explain, however, in detail, as we have seen, how the various normal modifications in the R group (Q, R, S) may occur by variations in the distribution of the impulse to the ventricle. It would seem that more experimental knowledge is necessary before we will be in a position to state exactly what anatomical structures are involved in this interpretation. We believe the evidence is sufficient at present to refer the R group mainly or exclusively to the process of conduction of the excitation. The question as to the exact structures involved we believe to be capable of experimental test and we hope to return to this in a later paper.

The T wave of the ventricle in the normal electrocardiogram we believe to be the expression of preponderance of contraction on one side of the line of equipotential. Whether this wave is directed in the same or the opposite direction to the R wave depends on a balance between the action current produced by the contracting muscle on each side of this line. The direction of the T wave and its size in either direction would seem to depend on (1) the position of the line of equipotential in relation to any given lead, (2) the extent of contraction of the ventricular muscle as a whole and (3) the relative degree of contraction in the basal and apical regions of the ventricle. The T wave is essentially a manifestation of contraction and occurs as a result of contraction of cardiac muscle from all parts of the heart. Its size and direction in the electrocardiogram is, however, modified by the factors named.

## BOOK REVIEW

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A TEXT BOOK OF PATHOLOGY FOR STUDENTS OF MEDICINE By J. George Adams, M.A., M.D., F.R.S., and John McCrae, M.D., M.R.C.P. (Lond.), illustrated with 304 engravings and 11 colored plates Lea & Febiger, Philadelphia, Pa., 1912

The task of preparing this book in one volume, which was evidently set on the shoulders of the authors by the publishers, is no small one. Dr. Adams and Dr. McCrae deserve great credit for having constructed out of the large text-book a single volume of so much merit. For it is not merely a condensation of the large treatise, but a text-book intended for a somewhat different purpose and, therefore, devised accordingly. An attempt has been made to present the student with the fundamental framework on which our ideas of diseases are based, and in doing this time and space have been devoted rather to a consideration of the general pathological processes and abnormal disturbances of physiology, than to minute and accurate descriptions of gross anatomical and microscopical lesions.

It follows, therefore, that the five chapters on "General Pathology," lead one almost half way through the volume of some 700 pages. The plan adhered to in the treatment of this section follows fairly closely that of the large volume. There has been, however, selection as well as condensation, and though in places the text would seem to be a little difficult for the beginner to follow, the concise descriptions are in the main clear, and to the point.

It seems to us, too, that the treatment of the special pathology has been very deftly arranged. Manifestly, it is impossible in a book of this size to furnish comprehensive descriptions of anatomical lesions, and, indeed, a good illustration is often worth pages of text. Such descriptions have therefore been relegated to a comparatively unimportant position, though of course mention is at least made of all departures from the anatomical normal. An excellent feature of this second part is a concise discussion of the pathological physiology of the various systemic diseases, which, after all, in such a treatise furnishes the student with a readable and fundamentally correct introduction to the subject. Thus in the chapter on special pathology of the blood and cardiovascular system about fifty pages are devoted broadly to pathological physiology, and thirty to morbid anatomy.

The introductory discussions to the chapters on diseases of the respiratory system, nervous system and urinary tract, though not so extensive, are also good, and to be greatly commended. The same method might have been carried out with perhaps more telling effect in the chapter on diseases of the digestive system, and a similar discussion, and short chapter devoted to diseases of the glands of internal secretion, would have added much to this second part.

One need not expect, therefore, to find in this book more than an outlined description of morbid processes *per se*, but he will discover a discussion, in framework, of active pathological processes, which serves as an excellent and readable introduction to the study of active diseases. Aside from the fairly numerous half-tones, there are two or three colored plates of really great beauty.

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## OBSERVATIONS ON THE COMPLEMENT FIXATION TEST FOR SYPHILIS WITH CADAVER SERUM

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NEW YORK

The question of the reliability of the Wassermann reaction as applied to post mortem sera, is an important one, not only from the theoretical, but also from the practical standpoint. The purpose of this paper is to review briefly the work already done along this line, and to report our own experiences with the Noguchi modification of the Wassermann reaction on sera obtained after death.

The literature bearing on the subject is nearly all German, and it is therefore in that country that there has arisen the most discussion and disagreement as to the value of the reaction. The question has hardly been touched on in American literature, and only recently in the English.

It was only two years after Wassermann made public his test that Frankel<sup>1</sup> and Much (1908) published the first paper on this reaction, as applied to cadaver serum. They used several varieties of antigen, obtaining consistent results with each. Of eighty-seven cases examined, they found thirty-seven positive (42.5 per cent). The positive results included five cases of scarlet fever. They concluded that the test was reliable and of great value in pathological anatomy. As a result of their work they considered mesoarteritis certainly luetic, but sclerosis of the testicle not always so.

A paper by L. Pick and Proskauer<sup>2</sup> appeared about the same time. They devoted most of their attention to cases showing some anatomical evidence of lues. Cases of benign stricture of the intestine, sclerosis of the testicle, smooth atrophy of the base of the tongue, aortitis, etc., were studied, and the conclusion reached that the test was a valuable asset to pathological diagnosis.

In the same year Bruch<sup>3</sup> came out against the reaction. He obtained fifty-nine positive reactions in 101 cases, among them a considerable

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1 Frankel and Much. *Munchen med Wchnschr*, 1908, lv, 2479

2 Pick, L, and Proskauer. *Med Klin*, 1908, iv, 539

3 Bruch. *Die Serodiagnose der Syphilis*, 1908, 47, *Fol Serol*, 1910, iv, 395



number in which there was no evidence of lues. He concluded that the reaction "*ist ein biologische, nicht ein cadaverische phenomenon*," and that it was unreliable when performed with post mortem specimens. Two years later he still believed that the test could never become reliable, because the error was not one of technic, but of serum alteration. He suggested the necessity of controlling the post mortem results by reactions done during life.

In 1909, Reinhart<sup>4</sup> reported thirty-five cases in which the results of the reactions coincided with his clinical and anatomical findings. The reaction was positive in his cases of mesoarthritis and sclerosis of the testicle.

Lohlein<sup>5</sup> published two papers in the same year and one in 1910. In all he covers nearly 500 cases. He obtained some anomalous negative and positive results. He admitted that there was a source of error somewhere, and was inclined to refer his positive reactions in cases giving no signs of lues, to this unknown error, rather than to latent syphilis. He thought that Bruch's results were due to the fact that the serum was not collected soon enough after death, a suggestion which Bruch partially accepted. He believed that only those cases should be considered positive in which there was complete inhibition of hemolysis. On the whole, he considered the test reliable and of value in pathological anatomy.

At the meeting of the German Pathological Society in Leipzig in 1909, at which one of Lohlein's papers was read, Schlimpert<sup>6</sup> expressed skepticism as to the value of the test. While acknowledging its specificity during life, he did not believe it could reach the same importance in cadavers. He reported forty-five positive results in a series of 261 cases. Nine of the positive cases gave no evidence of lues, eight, diagnosed as progressive paralysis, lacked anatomical verification, and one positive result was in scarlet fever. He acknowledged the possibility of latent syphilis in some of these cases, but thought that cachectic diseases might sometimes cause a binding of complement. He concluded that while the test was of high theoretical interest to the pathologist, it could attain a position of only limited practical significance in pathology.

Swift<sup>\*</sup> examined four cadaver sera and ten spinal fluids from cadavers by both the Wassermann and the Noguchi methods, and obtained better results by the Wassermann method. No anomalous positive reactions, however, were encountered in either series.

4 Reinhart. *Munchen med Wchnschr*, 1909, lvi, 2092.

5 Lohlein. *Verhandl d deutsch path Gesellsch*, 1909, xiii, Tag p 92, *Fortschr d Med*, 1909, xxvii, 97, *Fol Serologica*, 1910, iv, 227.

6 Schlimpert. *Verhandl d deutsch path Gesellsch*, 1909, xiii, Tag p 95.

\* Swift. *THE ARCHIVES OF INT MED*, 1909, iv, 376.

At a meeting of the German Pathological Society in Erlangen in 1910, Lucksch<sup>7</sup> reported a series of 300 cases, 50 per cent of which were positive. In nineteen, the test was controlled by ante mortem examinations, and in each instance the two were found to coincide. He believed that a pathologist could not depend alone on a positive reaction for the diagnosis of syphilis.

In the discussion following Lucksch's paper, Lubarsch<sup>8</sup> reported fifty-five positive reactions in 262 cases. In sixteen of these there was no evidence of syphilis. He considered the reaction valuable, but insisted on the use of several antigens.

Schmorl<sup>9</sup> strongly urges that only complete inhibition be considered positive. Marchand<sup>10</sup> agrees with Lohlein's views, and Simmonds<sup>11</sup> believes that positive results in non-specific cases are due to severe cachexia, sepsis, etc.

Veszpremi<sup>12</sup> has published his experience in 131 cases. Of these, thirty-one had to be discarded on account of changes in the sera which rendered them unfit for use. In the remaining 100 cases, he also performed many reactions on the spinal, pericardial, pleural, ascitic and hydrocele fluids. Of the sera, 46 per cent were positive. All but three of these agreed with the anatomical findings. The negative cases showed no clinical or anatomical evidence of syphilis. He gives a table showing the most frequent changes found in cases with positive reactions. Mesoarthritis ranks first, occurring in most patients over 40 years of age, next, chronic fibrous meningitis. In simple arteriosclerosis the reaction was always negative. Mixed cases of arteriosclerosis and mesoarthritis were most often found in later years (50 to 60), and gave positive reactions. In part he controlled his reactions by ante mortem tests, and found all in agreement excepting one case. The spinal fluid was never positive when the blood was negative, but in twenty-three of thirty-nine cases the blood was positive and the spinal fluid negative. The transudates agreed with the blood in about 90 per cent of the cases. He concludes that the Wassermann reaction can afford valuable aid in the solution of some contested problems in pathological anatomy. Lucksch, however, in reviewing this work, comes to a less favorable conclusion.

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7 Lucksch *Munchen med Wchnschr*, 1910, lvi, 1261, *Verhandl d deutsch path Gesellsch*, 1910, xiv, Tag p 249

8 Lubarsch *Verhandl der deutsch path Gesellsch*, 1910, xiv, Tag, 250. Discussion by Lucksch

9 Schmorl *Verhandl d deutsch path Gesellsch*, 1910, xiv, Tag, 250. Discussion by Lucksch

10 Marchand *Verhandl d deutsch path Gesellsch*, 1910, xiv, Tag, 250. Discussion by Lucksch

11 Simmonds *Verhandl d deutsch path Gesellsch*, 1910, xiv, Tag, 250. Discussion by Lucksch

12 Veszpremi *Centralbl f allg path u path Anat*, 1910, xxi, No 5 p 193

Kiefting<sup>13</sup> found that twenty-four out of ninety-six cases, in which syphilis could apparently be excluded, were positive. In another publication he found that this reaction threw valuable light on the cause of aortic insufficiency, the results of the tests corresponding almost always with the post-mortem findings.

Seligman and Blume<sup>14</sup> reported 100 cases. They used a number of antigens, and no test was considered positive unless there was complete inhibition of hemolysis with more than one of them. Although they had a few discordant results, they believed that the test was to be depended on, except where death was due to some wasting disease.

De Besche<sup>15</sup> obtained positive reactions in post mortem cases of tuberculosis, pernicious anemia and cancer. His natural inference was that the test was of a very limited value with cadaver blood.

Eich<sup>16</sup> investigated the problem with special reference to mesaortitis. He gave a favorable verdict.

Lubarsch<sup>17</sup> examined 623 sera, of which seventy-nine had to be discarded. Of the remaining 544, 109 were positive, of which forty-one gave no trace of luetic infection.

Nauwerck and Weichert<sup>18</sup> had to discard thirty-six of 243 sera. Of the remainder, fifty-seven were positive. They considered the method trustworthy and useful in pathological anatomy.

In October, 1911, von Weidert<sup>19</sup> gave a very comprehensive review of the whole question, with a full bibliography up to that time. He investigated 329 cases. Of these forty-seven were positive, 256 negative, and the rest doubtful or unsuitable for use on account of post mortem change in the serum. So he had positive reactions in 15.5 per cent of 303 cases, a low figure compared with Bruck's 58 per cent, Lucksch's 46 per cent, and Veszpremi's 46 per cent. Of the forty-seven positive cases there were twenty-five which were probably not syphilitic. He examined many of the cases microscopically and found that there still remained a tolerable number of anomalous positive reactions after every means had been employed to discover some trace of syphilis. He concluded that if only complete inhibition be accepted as positive, and that if sera from patients with cachectic diseases be discarded, the reaction was dependable, but of restricted value.

In March, 1912, Candler and Mann<sup>20</sup> in London reported on their examinations of 112 spinal fluids taken post mortem. In 92 per cent

13 Kiefting *Norsk Mag f laegevidensk* 1910, p. 65, *Deutsch med Wehnschr*, 1910, xxxvi, 366, cites *Centralbl f Path u path Anat*, 1910, xxi, 354.

14 Seligman and Blume *Berl klin Wehnschr*, 1909, xli, 116.

15 De Besche *Berl klin Wehnschr*, 1910, xlii, 1259.

16 Eich *Frankfurter Ztschr f Path*, 1911, vii, 373.

17 Lubarsch *Jahresb f aerztl Fortbild*, 1911, i, 67.

18 Nauwerck *Munchen med Wehnschr*, 1910, lvi, 2329.

19 Von Weidert *Cor-Bl f Schweiz Aerzte*, 1911, xli, 993.

20 Candler *Brit Med Jour*, 1912, i, 537.

of these the blood-serum was also investigated. Of the 112 cases of spinal fluid twenty-five were positive. All of the positive results were in cases of general paralysis, and in eight, positive reactions had been obtained during life. Three cases did not agree with the anatomical and clinical findings, but in these the spinal fluid was altered. They therefore obtained apparently correct results in 98 per cent of the cases with the sera. They observed anomalous positive reactions in 8.3 per cent. In a case of general paralysis dying of terminal streptococcus meningitis, the spinal fluid was negative. This strain of streptococcus, when inoculated into a known positive spinal fluid, deprived it completely of inhibitory quality. They therefore considered this the cause of one anomalous result.

The same writers bring out the point that infected or decomposed spinal fluids may not only give a positive reaction in a negative case, but that under the same circumstances a known positive case may be made negative. By using 0.5 per cent phenol as a preservative, they obtained constant results over a period of several months with the same specimen of spinal fluid. They concluded that the test is a very helpful one, but not so reliable as during life.

McIntosh and Fildes<sup>21</sup> in their book, gave a very concise review of the question up to 1911. They believe that some of the anomalous positive reactions are probably due to latent syphilis. As they consider post mortem sera to have more inherent power of inhibition than serum from living cases, they advise using somewhat less antigen than usual, and a control with twice the normal amount of serum alone. With these reservations they consider the test applicable to pathological anatomy.

In 1911, Wolff<sup>22</sup> of Amsterdam, published a paper on this subject, which was especially interesting in that it represented the first serious attempt to really discover the cause of the anomalous positive cases. Other investigators had attributed them to latent syphilis, or to changes in the serum which they did not attempt to explain. He attempted to discover the nature of this change. He was led to do this by his very bad preliminary results in which he obtained 50 per cent of anomalous positive reactions, and found a number of sera unfit for use. He was working under unfavorable conditions, such as warm weather, lack of cold storage, etc. He showed that these anomalous positive sera contain a larger quantity of inhibiting substance than fresh normal sera. He had to use a larger quantity of complement to obtain hemolysis after these sera had been added to the hemolytic system than was necessary with normal sera, known positive luetic sera from living cases, etc.

He then found that by adding  $\text{BaSO}_4$  to the sera (Wechselmann's modification of the Wassermann reaction), this inhibiting substance

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21 McIntosh and Fildes. *Syphilis from the Modern Standpoint*. London, 1911.

22 Wolff. *Ztschr f Immunitätsforsch*, Orig, 1911, xi, 154.

could be removed without otherwise affecting the reaction. It also made possible the use of some sera which previously had to be discarded. He investigated 260 cases by both methods. There were seventeen positive cases, six of which gave no trace of syphilis. In thirty-three further cases in which syphilis could apparently be excluded, he obtained positive reactions by the original Wassermann, but negative results after the addition of barium sulphate. After considerable further experimentation as to the nature of this inhibiting substance, he decided that it was a lipid, different from the substance causing the specific fixation of complement, but similar to the active ingredient of luetic liver extract. He believed this inhibiting substance could be removed by the use of barium sulphate, and that after such removal the test was of value in pathological anatomy. We have had no experience with this method.

From this review of previous work it is at once apparent that there is still a considerable difference of opinion as to the reliability of the test in pathological work. There are some points which we would further emphasize. In the first place, all workers have met with sera which were unfit for use and had to be discarded. Of course this makes any test impossible in such cases, and thereby imposes one restriction on the reaction in post mortem work. This condition of the serum is, in most cases, due to the time which has elapsed between death and the collection of the blood, and can accordingly be avoided in most cases by taking the serum sooner post mortem.

The limitation imposed by infection of otherwise good serum is not one which affects only the post mortem use of the test, for it is equally applicable to sera taken during life, it being well recognized that such sera give unreliable results. The anomalous negative results have not troubled investigators to any extent. They come fairly well within the range of similar results during life. In fact, the one great difficulty has been to explain the positive results in cases where syphilis could not be elicited from the history, or proven by the anatomical findings. All investigators have obtained these results. Even Wolff, who believed barium sulphate capable of removing the inhibitory substance, found that it did not do so in all cases. These anomalous positive reactions have been too frequent to permit of much faith in the theory of latent syphilis. While a few investigators have been distinctly skeptical as to the value of the test in pathological anatomy, the majority have, with certain reservations, considered it of considerable value.

Our own series of fifty-six cases is small. However, as there has been no interest shown in this phase of the Wassermann reaction in this country, and as these results represent the first reported extensive use of the Noguchi modification of the Wassermann reaction for this purpose, we believe it well to put them on record.

The cases may be divided into two groups as follows:

1 Positive Reactions	Cases
Syphilitic aortitis	3
Congenital syphilis	2
Cerebral hemorrhage	1
	<hr/>
Total	6
2 Negative Reactions	
Acute infectious diseases	10
Carcinoma	7
Diabetes mellitus	5
Marasmus	5
Chronic diffuse nephritis	4
Chronic endocarditis	4
Tuberculosis	3
Bullet wounds	3
Fractures	2
Cirrhosis of liver	1
Lymphatic leukemia	1
Aneurysm of thoracic aorta	1
Suppurative arthritis	1
Internal hemorrhagic pachymeningitis	1
Duodenal ulcer	1
Sarcoma	1
	<hr/>
Total	50

Of the six positive cases, five were unquestionably syphilitic, as shown by the histories and anatomical findings. The remaining case, a cerebral hemorrhage in a boy of 13, was quite suggestive. His mother had had four miscarriages. At the autopsy, an extensive hemorrhage was found in the right temporal lobe, and there was beginning atheroma of the arch of the aorta. Many large microscopic sections of the brain were studied, but they failed to show any signs of a glioma.

The histories and anatomical findings of the fifty negative cases were also carefully studied. In forty-nine there was no evidence of any kind to suggest syphilis. The remaining case deserves a little more consideration. It was a case of a large aneurysm of the thoracic aorta in a man 52 years old. There was absolutely no history of syphilis. He was under observation at the hospital over a period of three years, during which time three separate Noguchi-Wassermann reactions were found negative by three different observers. There was nothing found macroscopically or microscopically at the autopsy to suggest syphilis. As the post mortem reaction agreed with the three taken during life, it would seem that the results were perfectly reliable. In eleven of our cases, the reaction had also been done during life, and tallied in every case with the post mortem reaction. This method of controlling the reaction is the surest way of deciding on the reliability of the test.

Our work was done under favorable conditions. All but six of the cases were from the pathological department of the Presbyterian Hospital, where it was quite exceptional to have the body more than twenty-four

hours old at the time of collecting the serum. In most cases it was taken within a few hours of death, and, at times, while the body was still warm. In about five out of seven cases in which the body was more than twenty-four hours old, the serum had to be inactivated. The sixth case requiring inactivation was one of measles, and the other was the case of thoracic aneurysm, in which the serum was eleven days old at the time the test was done.

The six cases which did not come from the Presbyterian Hospital were from the morgue at Bellevue Hospital. There were also a few cases from this source which were not included in the above tables, as the sera were from bodies several days old and unfit for use. The blood was transformed from its normal structure into a thick viscid fluid, from which no serum could be separated by centrifuging.

In most of our cases the test was done within a few days of the time when the blood was taken. In only one was it postponed for over a week, and in this case inactivation was necessary. However, in this connection, it might be well to add that we have frequently found that when the active serum was kept on ice, it gave reliable results, even after two weeks standing.

In this work we have used the acetone insoluble residue of an alcoholic extract of human heart muscle as antigen. Dr. Noguchi has shown clearly that such an antigen contains less anticomplementary substance than the pure alcoholic extract. As practically all workers are agreed that one of the chief difficulties of the test lies in the increased inhibitory power of cadaver serum, it would seem particularly desirable in post mortem work to use an antigen as nearly free from anticomplementary substance as possible.

Most of the German workers have employed alcoholic extracts of syphilitic liver as antigen. We know of no previous work in which the acetone insoluble antigen has been used. Frankel and Much's satisfactory results were obtained with an alcoholic extract of normal liver. Bruch thought that possibly the difference between his results and those of Lohlein could be rectified by their using the same antigen. He therefore substituted an aqueous for the alcoholic extract, but still obtained the same unreliable results. Seligman and Blume used aqueous and alcoholic extracts of both syphilitic and normal livers. We believe that the acetone insoluble antigen is preferable for this work, and that its use will eliminate many of the discordant positive results.

Another factor of perhaps greater importance is the condition of the serum. As we have seen, in some cases, usually in subjects no longer fresh, the test cannot be done at all, as the blood has been transformed into a thick, gummy mass from which no serum can be obtained. In other cases, where the serum separates normally from the clot, it is

nevertheless infected, and, as with sera from living subjects under similar circumstances, the results are not dependable.

There is still another class of cases in which there is no visible change in the serum, but in which, nevertheless, there develops anticomplementary power in varying degrees. It is with these cases that investigators have had the greatest difficulty, and on account of which the test has been, by some, condemned. While we feel confident that the use of the acetone insoluble antigen in our cases has, to some extent, eliminated the difficulties inherent in these sera, we believe that it is important that more work be done to determine the nature of this inhibiting substance. A few of our cases needed inactivation on this account, but were perfectly satisfactory after the serum had been heated. In this small series of fifty-six cases our results have been most satisfactory. There is only one possibly anomalous positive result, that of the cerebral hemorrhage in a boy of 13 years. From our experience with the test we are inclined to the belief that the positive result in this case is strong confirmatory proof of the syphilitic nature of his disease.

In conclusion we may say that in the testing of cadaver blood—

1. The use of the acetone insoluble residue of alcoholic antigen is preferable on theoretical and practical grounds, to the pure alcoholic or aqueous extracts, for the reason that less anticomplementary substance is introduced.

2. The serum to be tested should be collected from the cadaver as soon as possible after death, and the test performed at the earliest possible date.

3. Infected and decomposed serum, from either the cadaver or the living subject, is not suitable for the complement binding test.

4. In this series of fifty-six cases, the Noguchi modification of the Wassermann test has given very reliable results.



# STUDIES OF RENAL FUNCTION IN RENAL, CARDIORENAL AND CARDIAC DISEASES \*

L G ROWNTREE, M D, AND R FITZ, M D  
BALTIMORE

Renal function has been studied in fifty-seven patients, the cases including pure nephritis, cardiac and cardiorenal diseases, the tests used being phenolsulphonephthalein, lactose, salt, water, potassium iodid and the accumulation in the blood of uncoagulable nitrogen. In certain cases, the excretion of indigo carmin and rosanilin was studied, as was also the glycosuria following the injection of phloridzin. It became apparent early that nothing was to be gained from the continued use of these dyes, as they were excreted roughly in proportions paralleling the excretion of phthalein and both much more slowly. Moreover, they were irritating to the patients. The use of indigo carmin was discarded also, because its colorimetric properties are not well adapted to accurate quantitative work<sup>1</sup>. The glycosuria following the administration of phloridzin seems to bear some relation to the excretion of lactose under similar conditions, i e., glycosuria is prolonged. Phloridzin glycosuria, however, is exceedingly variable under any conditions and it was considered more advantageous to use only lactose, on which greater reliance can be placed.

These tests were used with the following objects in view: (1) To estimate total renal function, (2) to determine the absolute and relative value of these tests in the diagnosis and prognosis of renal diseases, (3) in cardiorenal disease with varying degrees of chronic passive congestion and nephritis, to determine more accurately which factor is of greater importance in the causation of the clinical picture encountered, (4) to diagnosticate the presence or absence of impairment of renal function in cases in which clinically nephritis is suggested, (5) finally, to determine whether it is justifiable to draw conclusions relative to the involvement of the vascular or tubular functions under pathological conditions. In the majority of cases a limited number of tests were made. It is hoped that the cases will be followed over a longer period of time, and that repeated tests will be made to determine the progress of the disease. Such results will be published later.

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1 In this connection we agree with Oppenheimer (*Ztschr f Urol*, 1909, 111, 289), and disagree with Thomas (*Am Jour Med Sc*, 1911, cxlii, 376)

A brief outline of the purpose of the various tests, together with their technic, is given.

*Phenolsulphonephthalein* was introduced in 1910 as a functional test by Rowntree and Geraghty<sup>2</sup>. It is a drug devoid of toxicity and is eliminated almost entirely by the kidney. In health, following its intramuscular injection (0.06 gm.), 50 to 60 per cent is recovered in the urine in one hour and from 60 to 80 per cent in two hours.

From a study of a large series of cases including acute and chronic parenchymatous and chronic interstitial nephritis, and uremia, they concluded that where there was a marked decrease in output, marked renal changes were present. When the drug was continuously excreted in traces or not at all a grave prognosis was to be given, even without signs of uremia. The test proved of immense value in revealing the degree of destruction of renal substance, and of extreme importance in the estimation of total renal function for diagnosis and prognosis.

The test has been made according to the original technic.

#### TECHNIC

Patients were injected intramuscularly with 1 c.c. of a sterile solution containing 0.06 gm. of the drug. Each patient's bladder was emptied at the end of one hour and ten minutes and at the end of two hours and ten minutes. The urine was made definitely alkaline, diluted to 1 liter, and the amount of drug present determined by the use of Rowntree and Geraghty's<sup>3</sup> modification of the Autenrieth-Königsberger colorimeter.

*Lactose Test*—Schlayer<sup>4</sup> and his coworkers have studied the excretion of lactose, potassium iodid, salt and water in relation to renal function in experimental tubular and vascular nephritides, and in nephritis as exists clinically.

Lactose was shown by Voit<sup>5</sup> to be excreted quantitatively by the kidneys following its subcutaneous or intravenous administration. De Bonis<sup>6</sup> showed that it was well excreted by the glomeruli. Schlayer therefore adopted the time required for its elimination as a means of determining the vascular functional capacity in various forms of experimental and clinical nephritis. Since it is a substance foreign to the body, and consequently not subjected to the many extra renal factors which influence the excretion of water, he places his chief reliance on it as a vascular functional test. He admits that its excretion is delayed in passive congestion.

2 Rowntree and Geraghty Jour Pharm and Exper Therap, 1909, i, 579

3 Rowntree and Geraghty THE ARCHIVES INT MED, 1912, ix, 284

4 Schlayer and Takayasu Deutsch Arch f klin Med, 1910, xcvi, 17, Schlayer ibid, 1911, cii, 311, and 1911, ci, 333

5 Voit Deut Arch f klin Med, 1897, lviii, 545

6 De Bonis Giorn intern d science med, 1907, xxix, 446

As De Bonis did not claim that lactose was not excreted by way of the tubules, but merely that it was well excreted by the glomeruli, it seemed advisable to study more closely the mechanism of its excretion. As shown by Nussbaum<sup>7</sup> it is possible by excluding the glomerular system to obtain a urine from the frog's kidney which is solely due to tubular activity. By using this method we have shown in another publication that the tubules in the absence of the glomerular system are capable of excreting lactose.

From a repetition of Schlager's experimental work, from our own experience with lactose clinically as a functional test and from our recent studies of its behavior in experimental chronic passive congestion,<sup>8</sup> we feel that the mechanism of its excretion differs essentially from that of phthalein, salt, indigo, carmin, etc. In these studies, therefore, we have considered lactose, as did Schlager, an index to the condition of the vascular function of the kidney, admitting that we need much more information concerning the manner and significance of its excretion.

In these studies lactose has been prepared and injected as follows:

Two and five-tenths gm. were dissolved in 25 cc. of freshly distilled water placed in small cotton stoppered Erlenmeyer flasks and pasteurized for four hours for four successive days at 75 to 80 C. By this method the dose injected was slightly over 2 gm. in 20 cc. of water. A fresh solution was used for each injection and given according to the usual intravenous technic. Following injection no constitutional disturbances resulted save occasional slight headaches or malaise and in one instance a severe chill and fever for a few hours.

The normal excretion time for this amount is four to six hours. The urine was collected from the patients four hours after injection and every hour or two hours thereafter to twelve hours. Each specimen was tested by Nylander's reagent, using the same amounts of urine, solution, and length of time for boiling. In addition, in our earlier studies, polarimetric readings were made for total amounts of sugar regained. Since Schlager emphasized the time required for excretion as of chief importance, more recently we have merely determined this except where only traces were obtained.

*Salt and Water Tests*—The excretion of salt following its administration in amounts greatly in excess of that ordinarily taken with the food, is accomplished by the tubules, according to Schlager. Normally large amounts of salt are excreted by one of two methods. If the salt is given without extra water it is almost entirely excreted within twenty-four hours, without diuresis, by increased concentration in the urine, if given with an excess of water it is excreted partially through increased concentration in the urine and partially through diuresis.

Where, vascular injury to the kidney exists, the administration of salt may be followed by a marked diuresis, all of the salt being smoothly excreted in twenty-four hours without its percentage content in the urine.

7 Nussbaum. Pfluger's Arch. f. d. ges. Physiol. 1878, xvi, 179, 1878, xvii, 580.

8 Rowntree, Fitz and Geraghty. Unpublished.

being at all increased. This is usually associated with a somewhat low and fixed specific gravity, and the syndrome is spoken of by Schlager as vascular hyposthenuria. Here the inability to concentrate is not due to any incapacity of the tubules to excrete salt, but to hypersensitive vessels which respond to the salt administration with diuresis. In more severe vascular injury the vessels do not react in the same way, oliguria characterizing the urinary picture. In severe tubular destruction, a urine of fixed low specific gravity is obtained, the quantity of which is not materially affected by the administration of salt and the salt content of which is not augmented by administration of extra amounts of chlorids because of the inability of the tubules to excrete it. Such a condition Schlager calls tubular hyposthenuria.

The tests were performed as follows:

At the beginning of each study the patient was put on restricted liquids (2,000 cc) and a diet low in chlorids. A few cases were tried on salt-poor diet, e.g., 2.4 gm per diem, but it was found that immediately following this extra salt was usually poorly excreted, while the same patients on a diet containing more salt, e.g., 5 gm per diem later responded to added salt normally. The salt in the diet was estimated approximately by Locke's<sup>9</sup> and Brugsch's<sup>10</sup> tables. The urine was measured as passed, and total twenty-four hour specimens collected. The specific gravity was taken, and daily salt analyses made by the Lutke-Martius<sup>11</sup> method. When the salt output was found to be approximately constant for two days, in suitable cases, a salt test of from 5 to 10 gm was given. In this way when produced, a hyposthenuria and its type could be detected.

*Potassium Iodid Test*—Potassium iodid was one of the first substances to be utilized in connection with functional renal studies, being introduced by Duckworth<sup>12</sup> in 1867. It appears quickly in the urine following its administration by mouth, Quetsch<sup>13</sup> stating that it appears in nine to eighteen minutes after a 2 gm. dose, Roux<sup>14</sup> thirteen minutes after a 3 gm dose, and Studeni<sup>15</sup> thirteen to eighteen minutes after a 1 gm dose. The time required for complete elimination, as stated by different authors, varies markedly. According to Geisler,<sup>16</sup> 6 gm require twenty-five hours; Roux,<sup>14</sup> 5 gm require thirty hours, Studeni,<sup>15</sup> 1 gm requires thirty to thirty-six hours, Anten,<sup>17</sup> .5 gm requires forty hours, Schlager and Takayasu<sup>18</sup> and Monokow,<sup>19</sup> 5 gm requires forty-eight

9 Locke Food Values D Appleton & Co, 1911

10 Brugsch Diätetik innerer Erkrankungen Berlin, Julius Springer, 1911

11 Sahli Diagnostic Methods, 1911, p 455

12 Duckworth Saint Bartholomew's Hosp Rep, 1867, III, 216

13 Quetsch Berl klin Wchnschr, 1884, XXI, 353

14 Roux Thèse de Paris, 1890, No 248 Experiences sur l'élimination des iodures par l'urine

15 Studeni Untersuchungen über die physiologische Ausscheidung der jod Preparate durch den menschlichen Harn Dissert, Zurich, 1897

16 Geisler Quoted by Anten (See Note 17)

17 Anten Arch f Pathol u Pharmacol, 1902, XLVIII, 331

18 Schlager and Takayasu Deutsch Arch f klin Med, 1911, CI, 354

19 Monokow Deutsch Arch f klin Med, 1911, CII, 248

hours. Schlager, in his studies, did not consider, however, anything less than sixty hours to be a delayed excretion time following .5 gm by mouth. We have accepted this as a standard

According to the studies of Schlager, potassium iodid is excreted by the tubules of the kidney and on it he has placed most dependence in determining tubular functional capacity. Anten<sup>17</sup> showed that the excretion is not hastened by the occurrence of diuresis. It has been claimed by Schlager and Takayasu that its excretion is not influenced by chronic passive congestion and that it is not delayed in cases of cardiac decompensation, characteristics which, if true, would make it of tremendous importance in differentiating cases of pure passive congestion of the kidney from passive congestion associated with nephritis. Our studies,<sup>6</sup> however, on the excretion of potassium iodid in experimental chronic passive congestion show that it is often delayed in this condition. We feel, therefore, that for this purpose it is practically valueless.

Five-tenths gm of potassium iodid was given by mouth. Urine was collected at the end of forty-eight hours and tested every four hours thereafter until no positive Sandow's<sup>20</sup> test could be obtained.

*Determination of the Incoagulable Nitrogen of the Blood*—In 1821, Prevost and Dumas<sup>21</sup> found after extirpation of the kidneys an increase in the urea content of the blood. That this observation was of importance clinically in nephritis was recognized by Bright<sup>22</sup> in 1836. Since then many investigations have been made with the object of using the total incoagulable nitrogen or urea as a guide to prognosis and diagnosis.

By more modern technic, Ascoli<sup>23</sup>, Strauss<sup>24</sup> and others have found in severe grades of nephritis, the nitrogen, usually though not invariably, increased, the increase being much more marked toward death. Muller<sup>25</sup> believes that these facts in outspoken uremia are of the highest value, while von Noorden,<sup>26</sup> emphasizing the inconstancy of the findings, admits that the accumulation of nitrogen constitutes one of the important phenomena which result from renal insufficiency.

Obermayer and Popper<sup>27</sup> have found that cases of uremia show a

20 Sandow's test is made by taking 30 c c of urine, 2 c c of 2 per cent sodium nitrite solution and 2 c c of dilute sulphuric acid, adding chloroform and shaking. Purplish or violet color appears in the chloroform if iodid is present.

21 Prevost and Dumas. Quoted by Schöndorff. Pflüger's Arch f d ges Physiol, 1899, lxxiv, 307.

22 Bright. Guy's Hosp Rep, 1836, 1, 358.

23 Ascoli. Pflüger's Arch f d ges Physiol, 1901, lxxvii, 103.

24 Strauss. Die chronische Nierentzündungen in ihrer Einwirkung auf die Blutflüssigkeit und deren Behandlung. Berlin, 1902, Hirschwald.

25 Müller. Verhandl der deutsch path Gesellsch, 1904-5, vii-ix, Ergänzungsheft 80.

26 Von Noorden. Metabolism and Practical Medicine, 1907, 11, 486.

27 Obermayer and Popper. Ztschr f klin Med, 1909, lxxvii, 332.

much higher serum incoagulable nitrogen content than do normal individuals, or cases of nephritis without uremia, and that of this nitrogen, the urea fraction increases with the development of the uremia. Hohlweg<sup>28</sup> points out the importance of this latter observation, agreeing that though increase in urea is not specific for uremia, the demonstration of its presence in excessive amounts in serum affords an index of the renal functional capacity and thus is of value prognostically. Widal,<sup>29</sup> from an accumulation of his own observations in renal insufficiency, believes that it is generally possible to base on the degree of urea retention an approximate prognosis as to length of life, since patients persistently with more than 2 gm. of urea per liter of blood can usually live for only months or weeks.

In attempting to choose a method for estimation of incoagulable nitrogen or urea which is clinically practical, e g, simple, rapid and reasonably accurate, we have used and compared the following tests on blood or blood-serum:

1 Estimation of urea in blood by Widal's method 10 c c of blood are added to 115 c c of 95 per cent alcohol, 100 c c of the filtrate is evaporated to dryness, and the residue dissolved in the least possible amount of water. This is tested for substances decomposable by sodium hypobromite in a Doremus ureometer<sup>30</sup>. The amount determined represents that found in 8 c c of blood, from which the amount per liter is calculated.

2 The technic is the same as above, except that the residue following the evaporation of the filtrate is subjected to a Kjeldahl's nitrogen determination. The result represents that found in 8 c c of blood.

3 Estimation of total incoagulable nitrogen in serum by Morris'<sup>31</sup> modification of the Hohlweg and Meyer method. The procedure is as follows. To 10 c c of serum in a 300 c c Erlenmeyer flask is added a reagent consisting of equal parts of 1 per cent acetic acid and a 5 per cent solution of monocalcium phosphate until the reaction is acid to litmus but neutral to congo red. The volume is brought up with distilled water to 80 c c, and 80 c c of saturated sodium chlorid solution are poured into the flask. The mixture is boiled to precipitate the coagulable proteins, and the filtrate, from which the proteins have been shown to be completely removed, subjected to a nitrogen determination by Kjeldahl's method.

In a number of instances determinations were made by all three methods. The two latter gave nearly similar results. It was found that the first method in a control series of experiments, adding known amounts of urea to serum, gave an error of from 10 to 60 per cent, and therefore as a quantitative test was valueless.

Blood was used rather than serum (save in cases in which venesection was made), because it seemed that any increase of value prognostically would appear in the total blood as well as in serum. In the majority of cases Method 2 has been used. The normal figures are for total incoag-

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28 Hohlweg. *Deutsch Arch f klin Med*, 1912, civ, 216.

29. Widal. *Bull et mém d hôp*, Paris, series 3, 1911, xxxii, 627.

30 Widal used the Yvonne ureometer for this purpose.

31 Morris. *THE ARCHIVES INT MED*, 1911, viii, 457.

ulable nitrogen 500 to 600 gm per liter, and for urea .300 to 500 gm per liter of serum <sup>32</sup>

In the present state of our knowledge of renal diseases, classification of nephritis is difficult and unsatisfactory, and none so far suggested has met with universal acceptance or approval. Although clinically in certain instances it is possible to recognize acute, chronic parenchymatous or chronic interstitial nephritis, the autopsy findings repeatedly reveal processes different from those suggested in life. The internist is therefore inclined to confine his diagnosis to acute or to chronic nephritis, but even under such conditions the pathological study frequently demonstrates the presence of acute or chronic changes which were not suggested by the clinical study or history of the case, so classification on clinical-pathological grounds alone has proven unsatisfactory.

From his studies with the lactose, water, salt and iodid tests, Schlayer<sup>4</sup> has attempted to divide nephritis from a purely functional point of view

TABLE 1—CASES OF

Case No	Age	Clinical Diagnosis	Fluids	Urine	Sodium Chlorid			Sp Gr	Lactose (Hrs)	Iodid (Hrs)
					In	Out	Per cent			
337	57	Arteriosclerosis, chronic nephritis? Good condition	1600 1630	1400 1425	3.4 10	3.6 9.1	26 64	1012 1022	6 5.5	48 48
437	43	Brain abscess, hemorrhagic pachymeningitis, grave condition						†		
410	17	Orthostatic albuminuria,* chronic nephritis?	1540 2500	1555 1760	10 18	10.4 16.4	67 93	1013 1020	6.5	36

\*It is a question whether this case should not be placed in Group II. †Variable ‡Few hyaline casts

into four groups, e. g., pure vascular, vasculo-tubular, tubulo-vascular, and pure tubular nephritis. We have not used his classification because we feel that it is open to serious objections on the following grounds: (1) Our studies have led us to the conclusion that the potassium iodid test as used by him and on which he has placed greatest confidence for information regarding tubular functional capacity, is unreliable. (2) He has not described, nor have we encountered, any clinical cases which could be justly considered pure tubular nephritis. (3) The tests used cannot, we believe, determine accurately in the majority of cases where both systems are involved, whether the tubular or vascular injury is preponderant. (4) Mild passive congestion alone will in many instances produce the same functional picture which he describes as characteristic of vascular nephritis. Hence a combined clinical and functional study is

32 The technic in this test must be subjected to considerable refinement before conclusions based on slightly increased values (25 to 30 per cent) can be drawn.

essential in order to differentiate two functionally similar but clinically different conditions (5) Schlager has purposely not considered cases in which cardiac involvement was present. Since chronic nephritis is so commonly associated with cardiac or cardiovascular changes, whether causally or incidentally, we feel that in making a study of renal function, this group of cases should be considered.

Therefore, attempting to correlate clinical and pathological findings with the results of functional tests as simply and comprehensively as possible, the cases studied have been divided as follows:

Group I—Cases clinically suspected of nephritis<sup>33</sup> but exhibiting practically normal renal function

Group II—Cases of mild nephritis without cardiac decompensation

Group III—Cases of advanced nephritis without cardiac decompensation

Group IV—Cases of the cardiac decompensation and chronic passive congestion with or without nephritis

#### SELECTED NEPHRITIS

Phthalein	Urinanalysis			B P Sys	Nitrogen Blood	Urea Blood	Remarks
	Alb	Blood	Casts				
70	0	0	±	220	3	3	Renal function normal, patient improved
70	+	0	§	110 170			Renal function normal, tests exclude nephritis, patient improved
55	+	0	0	125	.	5	Patient left hospital with condition unchanged

Occasional casts

Besides these groups we have studied a few miscellaneous cases each of which will be described in detail (Group V)

#### GROUP I

It is seen from Table 1 that in these cases the increased salt is excreted normally almost completely within twenty-four hours through an increased concentration in the urine. The specific gravity is not fixed. Lactose and iodid are excreted in normal time, the phthalein output is not decreased, while the incoagulable nitrogen of the blood is within normal limits.

These cases are of interest in showing the value of such studies in renal function diagnostically. A brief history of each is given.

<sup>33</sup> The clinical diagnoses recorded in the accompanying tables were taken from the Johns Hopkins Hospital case records.



No, 82,337 Male, 57, white, married entered the hospital with the following history

He had always worked hard in business, with considerable worry His habits were excellent Three years before admission he was told that he had "diabetes" At intervals since various physicians had found sugar in his urine For years he had noticed slight nycturia He entered the hospital because, for six months, he had lost weight and strength and had been growing nervous

Physical examination was negative save for moderate cardiac hypertrophy, with an accentuated aortic second sound, and a soft systolic bruit transmitted from the apex to axilla His peripheral vessels showed a considerable degree of sclerosis His blood pressure was 220

The urine showed no albumin or casts, but a trace of sugar, which immediately disappeared under slight carbohydrate restriction

In brief, this was a case in which nephritis might be legitimately suspected, and if existent, to determine its degree would be of essential importance for prognosis, diagnosis and future treatment Functional tests showed normal renal function, hence the conclusion that his symptoms were due to arteriosclerosis, from which, so far, the kidneys had escaped to such a degree that function was not disturbed

No 82,437 A Russian tailor, 43, married, was admitted with the following history

Eight days before entry he had suddenly felt dizzy and fallen Since, he had had fever and sweating, considerable frontal headache, and a dry cough without sputum At times he was delirious, at times in stupor

Physical examination was negative save for a few fine crackles heard in both axillae on deep inspiration, absence of knee jerks, a positive Romberg's sign, and questionable Babinski's On the right there was a marked choked disk, on the left were scattered hemorrhages with the edges of the disk obliterated The blood-pressure varied between 110 and 170

The urine showed a trace of albumin and rare casts There was a temperature between 101 and 103 F

While the signs and symptoms pointed toward an intracerebral lesion, it was of utmost importance to demonstrate conclusively the entire absence of nephritis, or if any injury to renal function were present, that it was too slight to be responsible for the symptom-complex From functional studies there was no evidence of nephritis The patient gradually improved, and left the hospital with the diagnosis of brain abscess or hemorrhagic pachymeningitis

No 83,410 Boy, 17 years old, entered the hospital with a diagnosis of "orthostatic albuminuria" His mother died of some renal disease

His previous illnesses included chicken-pox and measles Until six months previously he had had constant "sore throat" which was relieved by tonsillectomy His habits were good

On admission he complained of frequent headaches, vertigo, nausea and vomiting of ten months' duration

His physical examination was negative except for distinctly palpable peripheral vessels His blood-pressure was 125 mm Hg

A trace of albumin was found in the urine, intermittently, but no blood cells or casts were seen

As indicated in the accompanying table (Table 1), his renal function was practically normal, the only suggestion of disturbance being the slightest delay in lactose excretion and a phthalein output slightly under the lower limits of normal. He is grouped among patients with normal function, tentatively. Repeated observations in such cases are unquestionably indicated, and it is hoped that further reports on these cases may be offered later.

#### GROUP II—CASES OF MILD NEPHRITIS

Nephritis in this group of cases is suggested clinically by some increase in blood-pressure, a slight cardiac hypertrophy, and palpable peripheral vessels, while albumin and casts may or may not be present in the urine. Functionally, the phthalein test indicates that the total renal excretory function may be normal, but is usually slightly decreased. A delay in lactose excretion, however, suggests vascular disturbance of function which may be corroborated by the associated "vascular hypostenuria" following the administration of salt. The specific gravity may or may not be fixed. The absolute salt excretion as well as that of iodid is usually normal. There is slight or no increase in the urea of the blood.

Opportunity has not been afforded to follow any one of these cases over a prolonged period of time, but it appears justifiable to suppose that such cases, if progressive, develop eventually into cases either of cardio-renal disease, or of marked chronic nephritis, i. e., Group II may pass over into Group III or Group IV. The data relative to these patients is presented in Table 2. Two characteristic cases are quoted.

Mr. X, aged 22, student, consulted Dr. F. J. Sladen, resident physician of the Johns Hopkins Hospital, on account of cardiac palpitation. Patient's father and uncle had died of nephritis. His previous history was unimportant, his habits good. Six months before examination patient noticed attacks of cardiac palpitation. Physical examination revealed a slightly enlarged heart, definitely thickened peripheral vessels, an occasional extrasystole, and a maximal blood-pressure varying from 140 to 150 mm. Hg. The urine showed at times the faintest trace of albumin but no casts were seen.

Functional studies showed normal phthalein, iodid and salt excretion, with a markedly delayed lactose. The urea of the serum was not increased.

No. 82,937. Male, 55, chemist, entered the hospital with an unimportant family and previous history. He had always worked hard and worried. His habits were excellent.

For some years he had noted nycturia, polyuria and mild attacks of nocturnal dyspnea. For one month he had felt "weak" and dull.

Physical examination showed that his heart was enlarged on percussion, with a rather heaving impulse. There were no murmurs. The aortic second sound was not increased. The peripheral vessels were thickened, with some atheromatous patches, and were tortuous. The fundi oculorum were negative. The urine showed no albumin or casts. The systolic blood-pressure was 166.

Functional studies showed a slightly reduced phthalein (40 per cent in the first 12 per cent in the second hour), a distinct diuresis following the increased ingestion of salt and a slight delay in lactose excretion, 10 hours.

Clinically these cases were instances of arteriosclerosis, but from functional studies it was shown that the total renal function in one, as indicated by phthalein excretion, was slightly affected, in the other normal, the delay in lactose excretion suggested vascular involvement, and diuresis in response to salt in one case that the vessels were hyper-sensitive. On the whole, these were cases of arteriosclerosis in which it was justifiable to assume that pathological changes had occurred in the kidneys, primarily of a vascular nature, but sufficient to interfere to some extent with some phase of renal function.

GROUP III—CASES OF ADVANCED NEPHRITIS WITH BUT SLIGHT  
CARDIAC INVOLVEMENT (TABLE 3)

As already suggested there is no sharp line of differentiation between this group and Group II, since in chronic cases there is a gradual transi-

TABLE 2—CASES OF

	Age	Clinical Diagnosis	Fluids	Urine	Sodium Chlorid			Sp Gr	Lactose, Hrs.	Kl, Hrs.
					In	Out	Per cent			
1	22	Arteriosclerosis, nephritis	1500	1000	9	8	8	1020	10	48
2	47	Chronic nephritis	1220	870	5	74	20	1015	10	48
3	24	Chronic nephritis	1140	1200	14	36	30	1010	6	40
			1130	800	3	33	13	1012		
			1140	700	9	70	100	1023		
7	55	Chronic nephritis, arterio- sclerosis	1120	1800	7	7	39	1011	10	48
			1360	2170	15	13	59	1012		

\*Patients all left the hospital with improvement of symptoms †Rare ‡At times

tion from the early stages of nephritis into this group or Group IV. Our acute cases, without doubt, must be included here on account of the results obtained by functional studies.

In this group, clinically, there was evidence of marked nephritis but none of cardiac inefficiency. The changes in renal function are therefore dependent on nephritis and not on chronic passive congestion.

The cases varied in severity. They have been grouped to show as far as possible, the gradual transition from nephritis with nearly normal renal function, to the most severe grades exhibiting uremia and ending in death.

In every case the excretion of water was either relatively or absolutely increased by additional salt, with three exceptions, and in only one was oliguria encountered. Certain of the cases were not given additional

salt, since from the clinical condition it seemed contra-indicated. In the cases tested, as a rule, salt was relatively well excreted through both increased concentration and polyuria. But in cases of the most advanced type it was constantly excreted in amounts less than administered and at the same time in low concentration. The specific gravity tended to be "fixed" and moderately low, except in one case.

Lactose excretion was delayed in all cases. In all but the most extreme cases there seemed to be no definite relationship between the excretion time of lactose, the severity of the disease clinically and the vascular hypersensitiveness, as determined by response to salt.

Potassium iodid excretion was delayed in the severest cases, but to an equal extent in two, which clinically were less advanced. Its excretion time did not seem to parallel absolutely the phthalein excretion nor the salt concentration, since the two cases in which the iodid was most slowly

## MILD NEPHRITIS\*

Phthalein		Urinalysis			B P Sys	Nitrogen, Blood	Urea, Blood	Remarks
1 Hr	2 Hrs	Alb	Blood	Casts				
60	80	++	0	0	150		176	No cardiac decompensation
	62	+		+	130		700	Patient on salt poor diet for a time. No cardiac decompensation.
30	51	+++		+	130		275	Received lactose intramuscularly. Amount recovered not estimated.
40	52	0		0	166		370	No cardiac decompensation.

excreted increased the salt concentration, following an additional 5 gm to the diet, and one excreted 45 per cent of phthalein in three hours.

As the disease became more advanced the excretion of phthalein constantly diminished. In patients with uremia, repeatedly, it was excreted only in traces or not at all for the two hours following injection.

The total incoagulable nitrogen and urea were increased in those cases which clinically and functionally had the most severe nephritis. Unfortunately, in one of the patients coming to autopsy no determination was made.

In five patients no lactose was recovered within twelve hours. Of these the four which were tested were unable to excrete salt either through increased concentration or through diuresis. Two showed a normal iodid excretion and two an excretion markedly delayed, four excreted only

TABLE 3—CASES OF CHRONIC NEPHRITIS

	Age	Clinical Diagnosis	Fluid	Urine	Sodium Chlorid			Sp Gr	Lactose Hrs	Solid, Hrs
					In	Out	Per cent			
	42	Chronic nephritis with acute exacerbation	1380	1115	2 1	3 80	32	1012	8	48
			1380	1065	7 4	8 17	76	1024	+	
	57	Chronic nephritis, mitral stenosis	1220	700	4 00	5 1	77	1015	12	48
			1220	675	9 00	7 1	1 10	1017		
	45	Chronic nephritis	1000	920	10	9 2	1 —	1018	10	48
1	55	Chronic nephritis	2610	2100				1012	*6	
			1960	2260				1016		
3	15	Chronic nephritis, brain tumor	1200	690	2 4	2 7	40	1017	12+	48
			800	730	7 1	6 3	87	1016		
0	51	Chronic nephritis, arterio- sclerosis	1610	1350	2 4	1 4	11	1013	*6	57
			1360	1300	7 4	3 00	22	1014		
1	8	Acute and chronic nephritis, mitral insufficiency, chronic tonsillitis	860	1000	5 00	3 00	30	1010	9	40
			480	400	3 00	8 9	28	1015		
7	51	Chronic nephritis, mitral insufficiency and myocar- dial insufficiency	1440	960	5 —	5—6	59	1020	12	
			960	1160	12 —	13 5	93	1017		
6	31	Chronic nephritis	2680	2350	9 —	9 1	40	1005	17	68
			3660	3320	12 —	13 2	40	1003		
1	28	Chronic nephritis	960	2350	8 —	8 2	35	1012	12	84
			1390	1550	4 —	5 0	31	1011		
3	50	Chronic nephritis	1060	1500	2 4	1 5	10	1012	12+	96
			1160	2400	7 4	5 5	23	1010		
01	24	Chronic nephritis, typhoid fever with hemorrhages from bowel and nose	1660	2030	10 —	12 —	60	1009	10	48
			1980	1860	8 —	8 —	42	1012		
58	52	Myocardial insufficiency, ar- teriosclerosis, chronic nephritis, uremia	2000	1650	5 —	7 —	42	1006	0	48
			2000	1700	10 —	6 8	40	1006	0	
	50	Chronic nephritis, uremia, arteriosclerosis	920	1640	8 —	3 —	18	1012	0	72
			1290	1225	5 —	2 —	16	1015		
	64	Chronic nephritis, arterio- sclerosis, myocardial in- sufficiency, uremia	940	1050	7 —	2 7	26	1016	0	72
			1110	1100	5 —	2 8	26	1012		
67	43	Acute nephritis, ulcerative endocarditis	1000	580	1 —	8 7	15	1012	0	
			1000	760	1 —	1 60	21	1009		

\*In one of these cases only a trace of lactose was recovered during these six hours Where no quanti-  
sent only in traces within the six hours and later not at all †Trace ‡Three hours §Rare

# WITHOUT CARDIAC DECOMPENSATION

Phthalein		Urinalysis			B P	Nitrogen in Blood	Urea in Blood	Remarks
1 Hr	2 Hrs	Alb	Blood	Casts				
15	45	+	+	+	180— 140	600	500	Left hospital improved
	42	+		+	180		850	Left hospital improved
25	40				208— 140	13	800	Untreated
	38	0	0	0	170		300	The amount of lactose recovered determined quantitatively treated in hospital
	37	+		+	270		600	Left hospital improved
	37	+	0	+	190— 160	728	600	The amount of lactose recovered determined quantitatively hospital improved
8	34—	++	+	+	80— 140			Phthalein repeated in 8 weeks showed 10 per cent for 1 hour, 30 per cent for 2 hours Left hospital improved
24	35	++		+	260— 190		300	Heart compensated Left hospital improved
17	27	+	§	+	240	400		Left hospital improved Died 6 months later No autopsy
†	45%	+	+	+	200— 130	400		Patient had edema Left hospital unimproved
5	7	+		+	210— 160			Left hospital improved
5	10	+		+	160		500	Second test two months after first Left hospital improved
—	†	+		+			14	
†	10	+		+	230— 270		185	At the time of test heart was compensated Left hospital unimproved
0	0	++		+	150— 180		500	Urea was determined 8 weeks later and was 140 Repeated phthalein test showed always traces for 24 hours Patient died in uremia Autopsy
0	0	+	0	+	230			When test made heart was re-compensated Two months later phthalein was 13 per cent for 24 hours Autopsy 3664 Chronic diffuse nephritis with an acute exacerbation
	†	+	+	+	110		120	Autopsy 3681 Acute ulcerative endocarditis Acute diffuse nephritis Healing kidney infarcts

tative study has been made an excretion period of six hours may be misleading since lactose may

traces of phthalein, the other, 10 per cent, for two hours. In four the incoagulable nitrogen or urea was markedly increased. In the fifth it was not tested. The three patients with lowest phthalein died, two in uremia within a few weeks, and one immediately with acute nephritis. The others have not been heard from.

The histories of a few characteristic cases are given.

No 81,952. Housewife, aged 42, entered with the following history.

Her previous history was unimportant save that three years before she had been in the hospital for three weeks with acute and chronic nephritis. Since then she had suffered from mild nycturia, precordial distress on exertion, and occasionally from headache.

Two weeks before entry edema suddenly developed, associated with severe vomiting. The urine became scanty and cloudy.

Physical examination showed a markedly hypertrophied heart. The aortic second sound was ringing; no murmurs heard. There was marked sclerosis of peripheral vessels and slight edema of the legs but no general anasarca or fluid in the serous cavities. The blood-pressure was 180. Urine at first was smoky, with blood, albumin and casts. Under rest this cleared up, leaving a slight trace of albumin and a few casts.

Her functional studies showed only a trace of lactose excreted in eight hours, though iodid and salt were normal. That total function was affected was shown by a lowered phthalein output (15 per cent for one hour, 45 per cent for two hours). The urea in the blood was not increased. Hence functionally as well as clinically she had well marked renal involvement which was not of great immediate significance. In the hospital her symptoms disappeared and she left much relieved.

No 80,891. Laborer, aged 24. For several years he had been bothered by nycturia, otherwise was always well.

Three weeks before entry he had been sick with fever, anorexia and nausea.

Physical examination was negative save for a faint systolic murmur at the apex of the heart, not transmitted to the axilla. The peripheral vessels were readily palpable. The blood pressure was slightly increased (140 to 160). The urine contained traces of albumin and a few casts.

The typhoid bacillus was obtained from blood; culture. The Widal reaction became positive.

The patient ran a severe and protracted course of fever, which was complicated by hemorrhages from the nose and bowel, reducing his hemoglobin to 18 per cent.

Eight weeks after entry his renal function was tested. It was found that the patient had a constant polyuria and "hyposthenuria" with salt normally excreted as to concentration and absolute amount. Lactose was excreted in ten hours, and 10 per cent of phthalein in two hours. The potassium iodid was excreted normally, there was no nitrogen increase in the blood. From the lactose and phthalein tests, evidently the patient had a severe nephritis.

A week later the temperature, which had been normal for ten days, suddenly rose and ran an irregular course for several days. A pure culture of typhoid bacilli was grown from the urine.

Six weeks later the patient had a severe attack of pain in the right flank with vomiting and fever. This subsided and was followed by an abundance of pus in the urine, disappearing in a few days.

The tests for renal function were repeated. It was found that iodid was excreted normally, salt, however, was retained, with no change in concentration on the addition of 5 gm. Lactose was not recovered at all, and phthalein only in traces two hours after injection. The urea of the blood had trebled. Functionally his condition had grown markedly worse, confirmed clinically.

Two weeks following the attack described the patient had another similar one but more severe, which was accompanied by delirium, fever and marked abdominal pain localizing in the region of the right kidney. This again subsided, accompanied by pyuria.

Ureteral catheterization was performed. Clear urine was obtained from both sides. Cultures from the right side showed the typhoid bacillus.

Finally, five weeks after the first attack of pain, the patient had a third similar one. It seemed advisable to operate. The kidney was exposed under ether and incised, but no recognizable pus was obtained. The patient improved rapidly, and was discharged in excellent condition. Unfortunately he has not been heard from since.

No. 90,899. Laborer, aged 64. Three years previously he was told that he had nephritis. Since then he had noticed nocturia and polyuria.

One month before entry he began to lose weight rapidly and become easily tired. Constant headache developed, and very recently shortness of breath. He noticed swelling in his feet for the first time at entry.

His physical examination revealed an enlarged area of cardiac dulness, with gallop rhythm at the apex, and a soft systolic blow over the aortic area. The aortic second sound was sharply accentuated. The peripheral vessels were markedly thickened and tortuous. The fundi were normal. There was slight edema of the extremities. The blood pressure was 190 to 230. The urine showed much albumin and many casts. The phthalein was 13.6 per cent for two hours.

Under observation and rest the edema disappeared, and the heart practically regained compensation. The general condition grew worse, however. Six weeks after the first test, functional tests were again made, showing only traces of phthalein excretion in two hours, no lactose in twelve hours and a delayed excretion of iodid and salt. The patient died in typical uremia. The diagnosis of nephritis was confirmed at autopsy.

Thus in cases of pure nephritis these tests are of value diagnostically in determining impairment of renal function, when clinically it is merely suspected. They are of value prognostically, for by repetition, especially of the phthalein test, it is possible to determine whether the disease is progressing, remaining stationary or subsiding. Moreover, patients with nephritis who continue to be unable to excrete phthalein, or lactose, and who show marked difficulty in excreting iodid and salt, usually die within a short time. Marked increase of the incoagulable nitrogen of the blood may afford additional positive evidence as to the severity of the disease.

#### GROUP IV—CASES OF CHRONIC PASSIVE CONGESTION WITH OR WITHOUT ASSOCIATED NEPHRITIS (TABLE 4)

The majority of our patients fall into this group. In so classifying them, a consideration of both clinical findings and functional studies is necessary in order to determine the relative responsibility of the heart and of the kidney for the existence of the symptom-complex. In this connection repetition of the tests is almost invariably necessary. One series of functional tests cannot always differentiate between the existence of nephritis or of chronic passive congestion. Experimentally,<sup>8</sup> it has been shown that in moderate degrees of passive congestion, as in nephritis, the excretion of lactose, iodid and salt may be interfered with. The excretion of phthalein may be normal but if the congestion is extreme it



TABLE 1—CASES OF CARDIAC DECOMPENSATION AND CHRONIC

No	Age	Clinical Diagnosis	Fluid	Urine	Sodium Chlorid			Sp. Gr.	Lactose, Hrs	KI, Hrs
					In	Out	Per cent			
21	48	Chronic nephritis, arterio-sclerosis, angina pectoris, myocardial insufficiency	800 900	600 600	2 4 7 4	1 2 3 2	20 51	1023 1023	10	48
116	47	Myocardial insufficiency Aortic insufficiency Arterio-sclerosis Chronic nephritis?	1200 1280	830 915	2 4 2 1	8 3 7 5	1 81	1023 1021	Trace in 4 hrs none later	72
31	48	Myocardial insufficiency Mitral reg and stenosis?	1200 1270	1015 1000	10 18	10 6 17 1	1 0 90	1017 1019		
55	49	Myocardial insufficiency Arteriosclerosis Mitral insufficiency	1120 1500	815 1005	5 10	6 5 11	86 1 1	1022 1026		48
52	61	Myocardial insufficiency, myocarditis, arterio-sclerosis	825 1025	1420 1350	2 4 2 4	15 6 16 2	1 1 1 2	1020 1021	7	
114	53	Myocardial insufficiency arterio-sclerosis, nephritis							12+	48
100	61	Arteriosclerosis, myocardial insufficiency	1260	780	6	11 7	1 5	1023	8	48
301	38	Myocardial insufficiency, mitral insufficiency, chronic nephritis	1130 1210	1855 1400	8 12	22 5 16	1 21 1 21	1012 1015	Trace 5	48
384	35	Myocardial insufficiency, myocarditis, arterio-sclerosis	1250 1250	615 680	2 1 5 1	3 5 4 5	57 66	1030 1018	8	60
012	54	Myocardial insufficiency, mitral reg and stenosis, arteriosclerosis	1085 1200	980 810	7 4 2 4	6 2 1 2	63 52	1014 1021	12	86
179	60	Myocardial insufficiency, myocarditis, arteriosclerosis, chronic nephritis?	1600 1600	880 830	7 1 2 4	3 6 3 5	42 43	1019 1020	12	48
670	59	Myocardial insufficiency, chronic nephritis, arterio-sclerosis	1525 1350	540 510	5 10	2 7 5	51 93	1020 1021	9	48
513	64	Chronic nephritis, arterio-sclerosis, myocardial insufficiency, cirrhosis of liver	960 960	150 1275	7 5	6 3 2	60 15	1015 1013	12	60
513	49	Myocardial insufficiency, aortic insufficiency, arterio-sclerosis	1200 1200	1126 954	5 7	4 6 4 5	41 48	1010 1020	9	68
544	73	Myocardial insufficiency, syphilis, arteriosclerosis, mitral stenosis, myocarditis, chronic nephritis	1240 1240	1550 2300	8	9 7	63	1016 1014	10	
392	45	Chronic nephritis, arterio-sclerosis, myocardial insufficiency	1210 1150	865 425	7 4 2 4	2 6 7 2	27 17	1017 1021	12+	
367	48	Myocardial insufficiency, mitral stenosis and regurgitation							12+	

PASSIVE CONGESTION WITH OR WITHOUT NEPHRITIS

Phthalein		Urinalysis			P B	Nitrogen in Blood Gms	Urea in Blood Gms	Remarks
1 Hr cent Per	2 Hrs Per cent	Alb	Blood	Casts				
47	79	+	At first but Clearing	+	170	6	7	Left hospital improved
56	76	+		Gran	180 130	16	12	Left hospital improved
51	70	+		0	160 180			Left hospital improved
	25 70	+		Rare	150		5	Second phthalein test two later Left hospital improved
32	54	0		0	120 150		6	Left hospital improved
	47	+		+	180 130		6	Left hospital improved
22	47	0		0	200 2		8	Left hospital improved
34	46	+		Few	160 170 140 1		5	Left hospital improved
	47	0		Few	120			Left hospital unimproved
23	45	+		+	180	700	6	Eight weeks later phthalein 45 cent for 2 hours N 600 L hospital improved
8	16 3 weeks 45 40	+		Rare	170 120	13	8	Left hospital improved
		+		+	180 120		3	Left hospital improved
	22 10 weeks 32	+		+	150 180		6	Patient died four months later A topsy 3766, tubercular polyse sitis, arteriosclerosis, cardiac h pertrophy, slight chronic diffi nephritis
17	37 22	0		Rare	150		3	Phthalein 22 per cent for 2 ho eight weeks later, after a break compensation Patient died A topsy 3738 syphilitic aortitis, c diac hypertrophy and dilatatio chronic passive congestion of a dominal viscera Kidneys show slight increase in connective tise between the tubules and thickeni of Bowman's capsule
19	35	0	0	Rare	140 1 180			Patient left hospital improved
17	34	++++		+	200		1	Patient left hospital unimproved
5	36	+		+	116 140		8	Patient left hospital improved

TABLE 1. CASES OF CARDIAC DECOMPENSATION AND CHRONIC

No	Age	Clinical Diagnosis	Fluid	Urea	Sodium Chlorid			Sp Gr	Lactose Hrs	Kl, Hrs
					In	Out	Per cent			
503	50	Myocardial insufficiency, mitral insufficiency, dilated aortic arch, arteriosclerosis							12+	48
590	53	Myocardial insufficiency, mitral stenosis, Dilated aortic arch, Pulsus irregularis perpetuus	1570	1055	5	123	118	1020	8	48
			1570	1275	8	155	12	1020		
182	50	Arteriosclerosis, myocardial insufficiency, chronic nephritis							10	100
123	50	Chronic nephritis and acute exacerbation, arteriosclerosis, myocardial insufficiency	1320	1325	8	57	30	1021	0	48
			1620	1325	8	51	37	1020		
861	58	Arteriosclerosis, myocardial insufficiency, myocarditis, arteriosclerosis	1550	2550	13	16	6	1020	10	15
			1270	775	8	9	6	1017		
305	45	Myocardial insufficiency, arteriosclerosis, chronic nephritis, uremia	1310	1005	3	5	50	1017	0	48
			1000	1000	3	8.5	85	1017		
782	63	Myocardial insufficiency, arteriosclerosis, chronic nephritis	1220	700	4	5.1	77	1076	12	48
			1220	675	9	7.1	11	1076		
732	39	Arteriosclerosis, glycosuria, chronic nephritis, myocardial insufficiency	1080	1325	15	11	1	1016		54
			860	775	5	2		1022		
055	48	Myocardial insufficiency, arteriosclerosis, chronic nephritis, dextrocardia	1570	1025	5	5.4	51	1021	12	48
			1320	1075	7	6.1	60	1011		
242	55	Myocardial insufficiency, chronic nephritis	1260	1760	7	4	23	1016	12	72
			1500	1715	5	3.7	22	1006		
899	44	Arteriosclerosis, chronic nephritis, cardiac hypertrophy and dilatation	1700	1775	24	31	17	1010	0	
			1780	1620	74	34	21	1014		
161	46	Chronic nephritis, uremia, myocardial insufficiency	900	1160	8	6.2	51	1012	0	72
			1000	1450	10	8.0	56	1008		

PASSIVE CONGESTION WITH OR WITHOUT NEPHRITIS—Continued

Phthalein		Urinalysis			P B	Nitrogen in Blood Gms	Urea in Blood Gms	Remarks
1 Hh Per cent	2 Hh Per cent	Alb	Blood	Casts				
18	27	+	+	+	130 160		7	Patient left hospital unimproved.
	30	+	0	+	130 1 160		3	Patient left hospital improved
7	32	+	0	+	210 1 160	500	600	Patient left hospital improved
27	44	+++	+	Pyal & Gran	160 1 140	1	1 2 1 3	Patient left hospital improved
15	27	+	0	Rare	170 1 160		6	Patient left hospital improved
0 13	Trace	+		+	216	63	6	Second phthalein test three weeks later Autopsy 3707 chronic subacute nephritis, chronic passive congestion
	24	+		+	220 180		400	Patient left hospital improved
17	27	+	0	+	?		81	Lactose not given on account of glycosuria Patient left hospital improved
7	20	+	0	+	150 120		3	Patient left hospital improved
0 15 18 12 5 5 15	Trace 30 28 20 10 —	+	0	Few	200 1 220		1 40	Died No autopsy permitted Second phthalein 10 days after first, third test after three weeks
		+	0	+	170 1 200	2 8	2 5	Patient left hospital improved
0	0	++		+	180 150			Died Autopsy 3664 Chronic diffuse nephritis with acute exacerbation Cardiac hypertrophy and dilatation

may be decreased. Therefore in experimental congestion, functional pictures indistinguishable from those of Group II and III described above have been found. The gradual amelioration of experimental congestion is accompanied earliest by an increased phthalein output, later by improvement in salt and iodid excretion, and lastly by a slight amelioration of the delayed lactose excretion.

Clinically, in passive congestion the tests behave in a similar way. By studying Table I, it is seen that in certain cases the functional results are identical with those obtained in an entirely different group (Groups II and III). It is seen that lactose is invariably delayed. Hence this test in such cases is of slight value. The specific gravity is not fixed, the quantity of urine varies depending on the degree of cardiac compensation. The excretion of salt varies. In certain cases there is retention, in others more salt is excreted than injected, either with "hyposthenuria" or increased concentration, or both. Potassium iodid, as a rule, is excreted normally even when nephritis is marked. Its excretion has been delayed strikingly, however, in four cases, in three of which the cardiac insufficiency played the major rôle. The fourth at autopsy showed an advanced nephritis. In the 6 cases with congestion and little or no nephritis the phthalein excretion is nearly normal, but as congestion becomes more marked it is decreased, returning nearly to normal with surprising rapidity as the cardiac conditions improve. If, however, there is a co-existent nephritis the phthalein excretion remains low, and does not improve markedly, despite improvement of circulation. In any case of nephritis with marked cardiac involvement, lactose, water, salt and iodid are vitiated as tests for renal function. By repeating the phthalein injection, however, information of great value may be obtained. *In the presence of marked nephritis the excretion of phthalein will remain low, paralleling the degree of renal destruction.* In those instances in which the excretion of phthalein is normal, or where after a decrease due to passive congestion, it has again become normal, nephritis may be entirely absent.<sup>34</sup>

In this class of cases the determination of nitrogen retention may be of value. According to Strauss and Hohlweg, incoagulable nitrogen and urea are increased in chronic passive congestion, but not so strikingly as in nephritis. Therefore, any marked increase gives valuable confirmatory evidence of extensive renal involvement.

The cases studied have been arranged in the table so as to show instances of pure chronic congestion and of slight nephritis, moderate

34 Such cases, particularly if exhibiting a normal salt excretion at the same time, may constitute a class of "Pure Chronic Passive Congestion." In our studies we have not described such a group, because we feel that clinical observations and functional studies should be made over a prolonged period before the existence of mild grades of nephritis can be excluded.

nephritis or advanced nephritis complicated by varying degrees of cardiac insufficiency and chronic passive congestion. A few illustrative cases are described.

No 82,216 Laborer, 47 years old, entered with an unimportant family history. Previously he had rheumatic fever, gonorrhea and syphilis (confirmed by a positive Wassermann reaction). At times he was a heavy drinker.

For ten years he had constant nycturia. For a year he had complained of dyspnea on exertion, with increasing weakness. For a month his feet were swollen. He entered the hospital because he was unable to keep up any longer.

Physical examination revealed a diffuse, heaving cardiac impulse, with area of dulness markedly increased. A systolic murmur was heard over the precordium, loudest at the apex, and transmitted to the axilla. Along the left border of the sternum was a diastolic murmur of slightly different pitch and intensity. The sounds at the base were soft. The second pulmonic sound was louder than the second aortic. The chests were dull at the bases and numerous râles were heard.

The fundi were negative. Albumin and casts were present in the urine at entry. The blood-pressure was 180. On the whole this seemed to be a typical case of cardiorenal disease, in which clinically it was difficult to determine the degree, if existent, of nephritis. Functional studies showed salt put out in larger amounts than taken in without diuresis, delayed iodid excretion, only a trace of lactose recovered. The phthalein output was, however, normal. From functional studies, therefore, there was disturbance in vascular function, with a normal total excretory function. Therefore clinically and functionally the patient showed marked cardiac weakness, with slight nephritic involvement. The subsequent history supported this view. The blood-pressure fell to 130, and the albumin and casts disappeared from the urine, the patient was discharged greatly improved.

No 82,755 represents another case of this description. The patient was a fishman, 49 years old. His father died of "heart trouble." The patient had always been well until a year before entry when his heart became irregular. Three months before entry he grew short of breath on exertion, the condition growing worse. Recently he had noticed nycturia and "swelling of his feet" during the day, which disappeared over night. He entered the hospital because he was unable to work any longer.

Physical examination showed a markedly hypertrophied and dilated heart, with an apical systolic murmur transmitted to the axilla. The peripheral vessels were markedly sclerosed. Examination of the chest showed dulness over both lower backs suggesting a moderate effusion. The liver was enlarged and tender. There was marked edema of extremities and genitalia. The urine showed albumin and rare casts. The blood-pressure was 150.

His functional tests showed no polyuria, salt well excreted by increased concentration, iodid normally excreted, lactose found only in traces for six hours, and none later. The phthalein was 25 per cent for two hours. Clinically the case seemed chiefly cardiac. A repeated phthalein test ten days later showed 70 per cent for two hours. In the meantime the albumin and casts had disappeared. The patient grew steadily better. Thus from a combined clinical and functional study it was clear that nephritis was absent, or if present, playing but a slight part in the clinical picture.

These cases bring up an interesting consideration. The delayed lactose and iodid excretion may be the result of cardiac weakness, and thus these cases may be of purely cardiac involvement without nephritis. This can only be determined by repeating the tests when compensation has been perfectly established.

No. 81,212 is a case of undoubted nephritis, combined with cardiac insufficiency. The patient was a tailor 55 years old. His family and previous history were negative save for two attacks of gonorrhea in youth.

Ten to fifteen years previously he had noticed spells of palpitation associated with weakness and giddiness. For several years he had complained of nycturia, and had been short of breath on exertion.

Eight months before entry he began to have attacks of nocturnal dyspnea, gradually followed by tenderness referred to the liver, and edema of the legs. For two months he had noticed marked loss of appetite and nausea.

The heart was markedly enlarged to percussion. A faint systolic murmur was heard along the left border of the sternum. The second pulmonic sound was slightly more accentuated than the aortic both with a ringing note. The peripheral vessels were sclerosed. The lungs showed signs of diffuse bronchitis. The liver edge on percussion was 5 cm. below the costal margin, not felt on account of the marked tenderness. There was edema of the extremities and over the sacrum. The urine showed a large amount of albumin and casts. The blood pressure was 220.

At the time the salt and water tests were made the patient showed a constant diuresis, with inability, however, to excrete salt. Lactose and iodid were delayed in excretion, phthalein was put out only in traces; the urea in the blood was increased. Thus functionally and clinically the patient was suffering from a failure of cardiac compensation, with marked nephritis. Under treatment cardiac compensation was largely regained. The lactose, however, remained delayed, the phthalein showed a slight relative increase, but persistently remained far below normal (never becoming more than 30 per cent. for two hours), and urea in the blood did not diminish. The patient died. Unfortunately no autopsy was permitted.

No. 82,923 is very similar. A laborer, 56 years old. His family and previous history were negative so far as known.

Two weeks before entry the patient was suddenly seized with chilliness, followed by precordial distress and cough. Three days later swelling of the legs was noted.

Physical examination showed an enlarged heart with marked arrhythmia. There were no murmurs. The aortic second sound was ringing. There was marked sclerosis of the peripheral vessels and edema of the legs which shortly disappeared. The blood pressure was 160. The urine showed albumin and casts in abundance.

Functional tests showed no polyuria, salt well excreted, and iodid normal. No lactose was excreted in twelve hours, 44 per cent. of phthalein for two hours. The urea of the blood was markedly increased. A week later the phthalein dropped to 30 per cent. for two hours, and two weeks later to 10 per cent. for two hours. The general condition had not improved, the patient showing toxic symptoms. After bleeding and sweating he became more comfortable and the phthalein rose to 25 per cent. for two hours. He improved clinically under rest, his phthalein, however, not increasing.

No. 82,303 is a case of advanced nephritis with cardiac dilatation and uremia. The patient was a barber, 43 years old.

His father had died of "dropsy and asthma." In his youth the patient had "children's diseases." For the past four years he had been a heavy drinker.

For six months he had noticed nycturia. For two weeks before entry he had suffered from "nocturnal dyspnea" which had finally become constant, and was accompanied by rapid onset of general edema.

Physical examination revealed a cyanosed, dyspneic man. The cardiac impulse was diffuse, heaving, and the area of dulness increased. A blowing systolic murmur was heard at the apex, transmitted to the axilla, and a murmur of different pitch and intensity at the base, transmitted to the vessels of the neck. A pericardial friction sound was heard at the xiphoid cartilage. The peripheral vessels were markedly sclerosed.

In the chest were heard numerous scattered râles. The liver was readily felt and was tender. There was marked edema of the extremities and sacrum, slight of the face and genitalia. The blood-pressure was 216 to 200.

Functional tests showed that urine was excreted in the same amounts as the fluid intake, with salt excreted in excess of the intake. Iodid excretion was normal. No lactose was recovered, and only a trace of phthalein in two hours. The nitrogen of the blood was not increased. Clinically and functionally the case suggested advanced nephritis with cardiac decompensation.

The patient's cardiac condition improved. The phthalein rose slightly (to 13 per cent for one hour). A month after this observation the patient suddenly developed convulsions and died. Unfortunately no functional tests were repeated, save a determination of total nitrogen in the serum, which was not increased.

Autopsy showed cardiac hypertrophy and dilatation, with marked chronic passive congestion and advanced subacute and chronic nephritis.

This case is interesting in showing that nitrogen determinations of the blood-serum may not be of value when negative, agreeing with the observations of Strauss,<sup>24</sup> who constantly found low figures in patients with chronic parenchymatous nephritis who died of uremia.

No 81,161 is a similar case. Laborer, 40 years old.

His previous history included measles, mumps and occasional attacks of tonsillitis.

For eight years the patient had been short of breath on exertion, and twice had had swelling of his feet.

He entered the hospital for gradually increasing dyspnea, orthopnea and edema.

The heart was enlarged on percussion, no murmurs heard. The aortic second sound was accentuated. The peripheral vessels were readily palpable. The lungs gave signs of diffuse bronchitis. There was shifting intra-abdominal dullness, and edema of dependent parts. The urine showed large amounts of albumin and casts. Blood-pressure varied between 180 and 150.

Functional tests showed frank polyuria, with salt fairly excreted. The excretion of iodid was, however, markedly delayed, and no lactose or phthalein were recovered. Therefore, functionally the patient had a marked nephritis. That nephritis was the important picture was supported by the facts that despite rest in bed and cardiac improvement, the phthalein was not excreted. The patient died with symptoms of uremia. The diagnosis of nephritis and cardiac insufficiency was confirmed at autopsy.

On the whole, studies of renal function in such cases are of the utmost value. If considered along with the clinical picture, and repeated at intervals, they furnish most valuable information regarding the relative responsibility of the heart or kidney in producing the clinical condition.

#### GROUP V—MISCELLANEOUS CASES

The cases in this group appeared atypical from the point of view of nephritis both clinically and functionally. The clinical diagnoses were cases of suspected syphilitic nephritis, of suspected amyloid nephritis, of nephrolithiasis, of polyserositis, and of carcinomatosis with Bence-Jones albumosuria. Each case is presented in detail.

No 81,373. Housewife, aged 27.

Her family and previous history were unimportant. She entered with a history of cough for two months, accompanied by shortness of breath, disturbances in



vision, nycturia, and loss of weight. Physical examination revealed a heart not enlarged, with a faint apical systolic murmur not transmitted to axilla or back. The lungs showed a slightly dull right apex over which were heard numerous coarse rales. The abdomen and extremities were not remarkable. From the facts that no tubercle bacilli were found in the sputum, that the Wassermann reaction was positive, and that at entry there was albumin and casts in the urine, it seemed possible that the renal condition might be syphilitic.

The functional studies are as tabulated. The patient was able to excrete salt and lactose normally, but the phthalein was only 38 per cent for two hours. Iodid was not given, since the patient was receiving the drug medicinally. However, under treatment the phthalein in a month was 60 per cent for two hours, the general condition had improved markedly, there were no longer casts or albumin in the urine. Therefore, it does not seem justifiable to class this patient among nephritics.

No 79,832. Lahorei, 30 years old.

TABLE 5—

Hosp No	Age	Clinical Diagnosis	Fluid	Urine	Sodium Chlorid			Sp Gr	Lactose, Hrs	Iodid, Hrs
					In	Out	Per cent			
1,373 (1)	27?	Syphilitic nephritis, acute bronchitis, tuberculosis?	1010 1060	1305 700	8 6	7.5 4.4	58 63	1013 1020	5	
1,832 (2)	30	Syphilitic arthritis, amyloid nephritis?	1560 2220	1100 1355	10— 13—	9.40 13.50	86 100	1016 1012	12+	50
2,004 (3)	42	Nephrolithiasis, renal colic, arteriosclerosis	1700 1500	620 855	5— 10—	4.1 6.00	67 71		4	36
1,925 (4)	32	Splenic anemia, polyserositis	1500 1500	1200 1250	8— 13—	6.6 5.5	55 46		5	50
2,971 (5)	35	Carcinomatosis	1040 870	900 700	5 14	1.3 1.3	15 18	1015 1110	8	72+

Entered with an unimportant family and previous history. Eight days before admission he complained of redness, heat and swelling in his left ankle, which ascended to the knee. On physical examination the heart was negative save for a systolic bruit transmitted from apex to axilla. Otherwise physical examination was negative except for the joint condition. The patient ran a protracted course of irregular fever, developing fluid or pus in various joints. The spleen became palpable, obscure signs in the chest and abdomen occurred. During observation the blood pressure steadily rose, albumin appeared in the urine, with many casts. Clinically amyloid nephritis was suggested.

The kidneys showed normal function save that the lactose was not entirely excreted within twelve hours, while the phthalein was on the lower border of normal (55 per cent for two hours), findings which suggested either a very mild nephritis or chronic passive congestion without nephritis.

The autopsy (No 3,713) three months later was especially interesting. There was a large retroperitoneal abscess walled off by a mass of chronic inflammatory tissue in which the capsules of the kidneys were imbedded. The kidneys were of normal size and grossly did not appear remarkable. Microscopically, however, they showed well marked congestion of capillaries without evidence of acute or

chronic nephritis It is suggested that the functional picture obtained was due to congestion caused by pressure from the abscess There is no positive proof The functional results, however, are identical with those obtained experimentally in mild passive congestion

No 82,004 Tailor, 42 years old

Family and previous history were negative save for small-pox and acute articular rheumatism in youth He had passed "renal calculi"

One week before entry he was suddenly seized with pain in the right flank, coming in attacks for variable lengths of time, radiating to the hypogastrium, and so severe as to require morphin

Physical examination showed a man slightly cyanosed and dyspneic His heart was not enlarged, but the aortic second sound was ringing The lungs were negative, the abdomen was negative save for slight tenderness in the region of the right kidney The blood-pressure at entry was 160, but rapidly fell to 130 The

# MISCELLANEOUS CASES

Phthalein		Urinanalysis			Nitrogen in Blood	Urea in Blood	Remarks
1 Hr	2 Hrs	Alb	Blood	Casts			
	38 60	+	0	+	700		Casts and albumin disappeared after treatment Patient left hospital improved
50	55	+	0	+			Patient died without symptoms of uremia Autopsy No 3713 C passive congestion
12	28	+	0	0	600	200	Urine cleared up after passage of stone Patient left hospital improved
20 55	70	0	0	0	308	280	Second phthalein test two days later Patient left hospital improved
13	23	+	0	0			Lactose intramuscularly Jones albumosuria Patient without symptoms of uremia autopsy

urine showed a specific gravity of 1,020, a trace of albumin, some red blood corpuscles and leukocytes but no casts On the day of discharge a freshly passed specimen showed no albumin, blood or casts

The functional tests showed the patient unable to excrete salt and having a low phthalein output (28 per cent for two hours) Lactose and iodid excretions were normal The patient passed calculi, but refused to remain in the hospital longer The decreased renal function in this case was probably due to the injury from renal calculi It is impossible to decide from the limited study of the case whether in addition there was a co-existent chronic nephritis, but the findings seem of sufficient interest to be reported in detail

No 81,925 Steward, 32 years old

Entered for the third time His family and previous history were negative He had entered the hospital seven years previously with the same history as at present, viz "Hemorrhage from the bowels and weakness" His previous diagnoses were variable It seems probable that the patient had either Banti's disease or a tuberculous polyserositis Physical examination suggested an adherent pericardium, there was an enlarged liver and spleen with ascites There was slight edema of legs The patient was markedly anemic, 26 per cent hemoglobin, 2 300,000 red cells

When first tested for renal function the patient was unable to excrete salt well, the phthalein was 20 per cent for two hours. Lactose and iodid were normal. A phthalein test repeated two weeks later showed 55 per cent for one hour and 70 per cent for two. It seems possible that salt excretion may have been disturbed in this case by extra-renal factors. The low phthalein in excretion may in part have been due to anemia, as at the second reading his blood condition had improved—Hgb now 55 per cent and 1,000,000 R B C. Considering the later test and other results, the impression is that the patient had no nephritis.

No 82,971 Housewife, 35 years old<sup>35</sup>

The patient's father died of "cancer." She had always been well until six months before entry, when she noticed pain in her right hip. Two months later her left hip became tender, a month later she noticed a small mass in her right breast which grew rapidly in size.

In the last few weeks she had grown very weak, since her illness began she had lost 40 pounds in weight.

Her physical examination was negative save for a tumor of the right breast with involvement of sacrum, iliac bones, femur and fibulae. There was a suggestion of involvement of the frontal bone and spine. The urine contained Bence Jones protein but no blood or casts. Tests of renal function showed that the patient was unable to concentrate salt or to excrete it through diuresis, to excrete iodid or phthalein normally, while her lactose was slightly delayed. The functional results here suggested more than any others obtained a tubular nephritis with tubular hyposthenuria. The patient died, but there was no autopsy permitted, therefore the significance of these findings can not be determined.

On the whole, this group is of interest as illustrating certain atypical findings. It is difficult to interpret the cases and results more thoroughly.

#### GENERAL SUMMARY

Our studies permit of the following summary and deductions.

1 In the group of cases studied the quantity of urine has been variable. There has been no constant relationship between the existence of polyuria or oliguria and the condition of the patient as determined by other functional studies or clinical observation.

In cases with cardiac involvement the amount of urine has been exceedingly variable apparently depending on the degree of myocardial insufficiency, edema or other extra-renal influences. Hence, the quantity of urine was of little value in determining the condition of renal function.

2 The specific gravity of the urine in the most advanced cases of nephritis has been constantly low, in other cases variable. In general, cases with cardiac decompensation have shown a urine of higher specific gravity than those with pure nephritis, and cases of advanced nephritis with cardiac insufficiency have shown a less concentrated urine than cases of cardiac insufficiency with little nephritis.

3 Sodium chlorid added to the diet in considerable amounts has been excreted normally in the majority of cases studied. In advanced nephritis it has been excreted in amounts less than those ingested. In neph-

<sup>35</sup> Reported by Drs Boggs and Guthrie, Bull Johns Hopkins Hosp, December, 1912.

itis with cardiac decompensation its excretion has varied, certain cases retaining it — whether or not complicated by edema — others of more advanced nephritis clinically and functionally, excreting more than ingested

Moreover, these studies have suggested that patients who have been on a salt-poor diet for any considerable length of time, are unable to excrete added amounts readily, irrespective of the cardio-renal condition. Therefore, the study of salt excretion alone, as a test for renal function, is of little value. Its value consists in affording corroborative evidence to other tests, but owing to the many extra-renal factors to which it is subjected, its absolute value is slight.

4 Lactose excretion has been delayed in all cases of nephritis or chronic passive congestion. Cases in which no lactose has been recovered in the urine within twelve hours after injection were clinically instances of severe nephritis. Although the failure of lactose to appear in the urine is of considerable value prognostically, we do not feel that the number of hours necessary for complete elimination is a valuable index of the renal condition.

As already indicated, the mechanism of its excretion is not determined, although it must differ essentially from that of iodid, salt or phthalein. A marked delay in its excretion suggests a disturbance of renal function which may be manifested in no other way. Its exact significance is unknown.

5 The potassium iodid excretion has varied markedly. In the cases of most marked nephritis it has been delayed. In cases of congestion clinically suggesting but little nephritic involvement, it has also been delayed. In one case clinically of advanced nephritis (confirmed by autopsy) it has been normal. There seems to be no constant relationship between the degree of nephritis or of congestion and the excretion of the drug. Hence its time of excretion as a test for renal function is practically worthless.

6 Phthalein has been excreted in amounts paralleling the degree of functional involvement of the kidney, as indicated by the clinical condition, subsequent history, or autopsy. In marked chronic passive congestion without nephritis it has been low at first, but has returned rapidly to normal with improvement of circulation. In cases of chronic passive congestion with nephritis its excretion has remained persistently low apparently indicating the actual functional capacity of the kidney.

Therefore, the phthalein test for renal function has afforded the most reliable information as to renal efficiency and has been of great value in differentiating functional incapacity due to nephritis from that due to chronic passive congestion.

7 The marked accumulation of incoagulable nitrogen in the blood when present is valuable evidence of renal insufficiency. How great the value of this test is we are unable to state from our own experience.

Our cases which correspond to those studied by Schlayer are considered in Groups II and III. The first are of "vascular nephritis" predominantly. This is evidenced by a delayed lactose excretion accompanied in one case by "vascular hyposthenuria" and diuresis. Tubular function was normal as indicated by the ability to concentrate salt and by a normal iodid excretion.

The cases of Group III would fall into either his groups of "tubulo-vascular" or "vasculo-tubular" nephritis. Lactose excretion is delayed, in many instances there is hyposthenuria of a mixed type. The tubes are involved as shown by their inability to concentrate salt and in certain cases by a delay in the iodid excretion.

The chief importance in studying cases in this way is the ability afforded to recognize as early as possible abnormalities in renal function, and by repeating these tests over intervals of time to follow the subsequent course of the disease in any individual patient. For practical purposes it seems from these studies that in advanced nephritis the phthalein and incoagulable nitrogen tests give more definite and reliable information prognostically than the others used, in early cases or suspected cases, the lactose, iodid and salt tests may prove of value.

#### CONCLUSIONS

1 *The functional condition of the kidney can unquestionably be determined much more accurately by the use of these tests than through ordinary clinical studies alone.*

2 The phthalein test is of great diagnostic and prognostic value. For general use it is of more value prognostically than any other single test, diagnostically, also, it is of value in cardio-renal disease for determining the relative responsibility of the heart or kidney for the clinical condition.

The lactose test is of great value diagnostically in determining the existence of abnormal renal function. The significance of its delayed excretion is obscure. The suppression of the excretion of lactose may be of considerable value prognostically.

The salt test if considered alone is of no value, since it is subjected to so many extra-renal factors. When considered in conjunction with clinical and other functional studies, it may prove of some value diagnostically and prognostically.

The amount of water excreted in cases of pure nephritis in response to sodium chlorid stimulation may be of diagnostic value.

The potassium iodid test is of little value diagnostically or prognostically.

The marked accumulation in the blood of incoagulable nitrogen, in cases of nephritis when present, is of considerable prognostic value

3 It is possible in cases of cardiorenal disease with varying degrees of chronic passive congestion and nephritis to determine which factor is of greater importance in the causation of the clinical picture encountered. This can be done most readily by repeated phthalein tests, while the determination of incoagulable nitrogen in the blood may also be of value. The lactose and iodid tests are of no value in this respect.

4 It is possible by these tests to diagnosticate the presence or absence of impairment of renal function in cases in which clinically nephritis is suggested. In this respect the lactose and phthalein tests are of most value.

5 Before feeling convinced of the justifiability of drawing conclusions relative to the involvement of the vascular or tubular functions under pathological conditions, we feel that a much deeper knowledge concerning the physiology of the excretion of these various substances studied is necessary.

It is with the greatest pleasure that we acknowledge our indebtedness to Dr Barker, Dr Thayer, and the other members of the medical staff of the Johns Hopkins Hospital for their cooperation and interest in this work. To Dr Thayer we are particularly grateful for many helpful suggestions and for clinical material.

# EXPERIMENTAL OBSERVATIONS ON THE EFFECTS OF THE ADMINISTRATION OF IODIN IN THREE CASES OF THYROID CARCINOMA (TWO HUMAN AND ONE CANINE)

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There is no doubt that in the development of normal tissues structural differentiation and functional differentiation parallel each other, but in the case of tumors little is known as to whether any such parallelism exists. One obvious reason for this is that very few of the tissues from which tumors most frequently develop have any readily estimated physiological attributes. Beginnings have been made in this direction in the case of adrenal tumors (hypernephromas) through investigations for the presence of the specific pressor substance<sup>1</sup>. So also considerable work has been done with lipomas by way of chemical analysis and comparison with the fat of normal adipose tissues<sup>2</sup>. For investigations in this field it has long seemed to us that the thyroid offered most favorable conditions. Thus its architecture is simple, it is localized, easily accessible and has a wide range of morphological variations within the limits of normal functional activity. In man it is one of the most frequent sites for tumor development, particularly the adenomas. The most favorable factor, however, is that the easily determined iodine offers a fair test for the functional activity of this tissue. Thus it is well known that iodine to a marked degree controls the morphological changes associated with the physiological variations and overgrowths in the gland and also that iodine is an essential constituent of the active principle of the gland's secretion. It is on the basis of a rather extensive experience with the relation of the iodine content to gland structure and on the comparative effects of iodine on the thyroid in various phases of physiological activity that some years ago one of us undertook the study of the relation of the iodine content of benign epithelial tumors (adenomas) to their histological structure and of the effect of the administration of iodine on such tumors in comparison with its effects on the adjacent non-tumor thyroid. Some of these observations have been published<sup>3</sup>. Summarizing briefly it was

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1 Brooks Jour Exper Med, 1911, xiv, 550

2 Wells THE ARCHIVES INT MED 1912, v, 297

3 Marine Jour Med Research, 1913, xlvii, 228

found that all benign epithelial tumors have some capacity for iodine, but that this is always much below that of the adjacent non-tumor thyroid. There are variations in the capacity of these tumors for iodine which in a general way run parallel with the degree of morphologic differentiation. Thus simple adenomas or the most differentiated group have the greatest capacity, approaching closely in some instances to that of the non-tumor thyroid tissues, while the fetal adenomas, or the least differentiated have the least capacity for iodine. In the interpretation of these findings it was suggested that benign epithelial tumors of the thyroid are only partial tumors, in that they still have preserved, to some degree at least, one easily detectable, physiological attribute of the non-tumor thyroid tissue.

In view, therefore, of the well-known iodine relations in the simple non-tumor functional hyperplasias (goiter) and of the findings in the benign epithelial tumors, it seemed of importance to extend these observations to include malignant epithelial hyperplasias of the thyroid. During the past year two opportunities for such observations in man have occurred, and it is through the courtesy of Drs C A Hamann and E P Carter, in whose services at the City Hospital the cases were admitted, that we have been able to observe and follow them to their termination. In both cases a portion of the thyroid tumor was removed several months before death, iodine was administered for a long period of time and autopsies were obtained. Abstracts of the cases follow.

#### ABSTRACTS OF CASES

CASE 1—J K, City Hospital No 11766, admitted November 2, 1911. Male, Pole, aged 37, laborer. Owing to poor interpretation only a partial history was obtained.

Complaint. Enlargement of the neck with pain.

*Physical Examination*—Patient was well developed and fairly well nourished. There was slight bilateral prominence of the eyes, no tremor, no tachycardia. General glandular enlargement with an increase in the size of the thyroid involving both lobes and the isthmus. The thyroid was somewhat tender on pressure and on deep palpation was slightly nodular. Admission temperature 102.3 F, pulse 80, respiration 18. Thyroiditis was suspected. Blood Examination. Hgb 85 per cent, R B C 4,200,000, W B C 8,600. Differential count. Polymorphs 67 per cent, mononuclears 10 per cent, lymphocytes 17 per cent, eosinophils 1 per cent, transitionals 5 per cent. Urine on November 16 showed a trace of albumin.

November 5, 1911, measurement of neck in largest circumference 42 cm.

November 12, 1911, measurement of neck in largest circumference 40 cm. Temperature 98 F, pulse 90, respiration 20. The thyroid at this time was distinctly nodular and apparently adherent to adjacent structures. A small nodule was made out just above the clavicle on the left side. Malignancy was suspected at this time.

Nov 14, 1911. Syrup of ferrous iodide was begun in doses of 8 minims t i d. The condition of the patient remained but little changed until November 25 when Dr Hamann removed the left lobe, isthmus and part of the right lobe.



*Pathological Report*—Right lobe and isthmal portion The mass is hard, slightly nodular and covered with numerous tags of tissue from the separation of fibrous adhesions. It has neither the shape nor the general appearance of thyroid. Weight of mass 76 grams. On section the surface nodules are found to be adenomatous masses five in number, the largest measuring 3 by 3 cm. One contains calcareous deposits, another is cystic, and the smaller ones are glandular throughout. These adenomas are imbedded in a hard, white scar tissue throughout which are yellowish, necrotic areas varying in size from 1 mm to 6.8 mm. These areas resemble the caseation seen in certain types of tuberculosis or actinomycosis. No true thyroid parenchyma is made out. The general appearance is that of a chronic inflammatory process in a pre-existing adenomatous goiter.

*Microscopic Examination*—Sections from seven areas of the tumor mass were studied. In only one was there evidence of non-tumor thyroid tissue and this was very sclerotic, with small, shrunken follicles. Sections through two of the adenomas revealed characteristic adenomatous structure composed of small, uniform, closely set colloid-containing follicles in the subcapsular zone with atrophy and hyaline degeneration of the central portion. The non-adenomatous tissue is for the most part dense, infiltrated fibrous tissue with scattered islands of tumor cells occupying clefts and quite frequently filling the lumina or veins. These tumor areas correspond to the necrotic yellowish areas noted in the gross specimen. The cells are uniformly distributed throughout a given tumor area with no differentiation into follicle formations. The cells are highly irregular in size. Their nuclei are irregular in size and staining intensity, resembling sarcoma as much as carcinoma. Hemorrhage and necrosis are present in all the larger areas. In a few of the areas suggestive follicle formations are present owing to the presence of very scant stroma. On this account the possibility of the tumor being one of those rare sarcomas comparable to those described by Wells<sup>4</sup> in the dog, by Leo Loeb<sup>5</sup> in the rat, and Woolley<sup>6</sup> in man, was considered. Almost all of the described cases of this double tumor have been primary thyroid tumors. A study of the metastases in our case eliminates this possibility.

Dec 1, 1911 Wound healing, back rest, temperature 98 to 99 F, pulse 90 to 100, respiration 18 to 20.

Dec 8, 1911 Sodium iodid grs 3 t i d substituted for the syrup of ferrous iodid. Wound healed, temperature normal, pulse 80 to 90, respirations 20.

Dec 18, 1911 Patient complains of pain in the right thigh and knee. A small mass on the inner side of the right ilium was made out. X-ray plates at this time were negative.

Dec 23, 1911 Patient's general condition fair. Was discharged.

Jan 2, 1912 Patient readmitted complaining of pain in the region of the eighth rib in the right axillary line and in the right hip. Physical examination shows no noteworthy change in the neck region. There is a small palpable tumor mass attached to the eighth rib in the axillary line and a tender mass in the right inguinal region. The face had a sallow, puffy appearance. There is increased dullness over the manubrium. The superficial veins of the thorax and abdomen are becoming prominent and somewhat tortuous. An x-ray plate taken at this time shows mediastinal growth extending to the left and to the right of the base of the heart, also a mass in the left ninth rib posteriorly.

Jan 11, 1912 Complains of pain in the right inguinal region and in the right arm. The face is cyanotic and edematous, veins of the neck very much distended.

Jan 15, 1912 Patient is quite ill, face greatly enlarged and cyanotic. The temporal veins are much distended. Motor power on the right side is decreased. Reflexes diminished. Right arm swollen.

<sup>4</sup> Wells, H. C. Jour Pathol and Bacteriol, 1901, vii, 357.

<sup>5</sup> Loeb, Leo. Am Jour Med Sc, 1903, N. S. cxv, 243.

<sup>6</sup> Woolley, P. C. Am Med, 1902, iv, 331.

Jan 16, 1912 Tongue enlarged Speech and swallowing difficult Morphine  $\frac{1}{4}$  two to three times per day necessary to control pain

Feb 24 1912 The mass in the right inguinal region had progressively enlarged Superficial veins of the abdomen and thorax have undergone further enlargement and edema of the face, tongue and neck region is very much lessened

March 16, 1912 Patient had lost much weight, most marked pain now is in the thorax Well developed collateral circulation around the obstructed superior vena cava

April 9, 1912 Obstinate constipation, great emaciation, continuous pain, anxious pinched appearance, catheterization necessary

April 19, 1912 Patient died this morning Autopsy three hours later

*Autopsy Report*—Body length 170 cm Marked emaciation, rigor mortis present

Old thyroidectomy wound The laryngeal cartilages and neck muscles are obscured by diffuse subcutaneous thickening There is marked tortuosity of the veins of the chest and abdomen A large rounded mass about 12 cm in diameter in the right iliac fossa The right leg muscles are distinctly atrophic

Internal On removing the sternum the tumor mass was found to involve the manubrium and both clavicles No excess of fluid in the pleural cavities The thymus area is replaced by tumor tissue which is continuous with the thyroid area above Right lung free from adhesions and air-containing Many nodules varying from 1 to 5 cm in diameter are scattered throughout the lung No consolidation Bronchi reddened and contain some mucopurulent exudate Left Lung Few adhesions at apex and near the base, air-containing Multiple tumor nodules of approximately the same size and distribution as in the right lung These tumor nodules are grayish opaque in color Many of the masses have central areas of necrosis In the eighth rib on the right side there is a fusiform swelling which on section proved to be a medullary metastasis On the left side springing from the ninth rib is a hemispherical mass 4 by 5 cm in diameter projecting into the pleural cavity but completely covered with pleura

Heart Pericardial surfaces smooth There is no excess of fluid Heart muscle soft and flabby The superior cava is completely blocked by tumor growth, distending the vessel to a diameter of 2 to 2.5 cm and extending up into the innominate and down into the right auricle Pulmonary veins, inferior cava, aorta, and pulmonary artery free Liver Normal appearance, free from metastasis Spleen Slightly enlarged Malpighian bodies and trabeculae prominent Kidneys Right measures 11 by 6.5 by 4.5 cm Capsule strips readily On the surface are many yellowish raised spots distributed over the entire cortex On section the surface spots extend through the cortex as yellow streaks Left kidney similar in all respects to the right Adrenals normal Pancreas normal There is a small metastasis in the mesentery of the transverse colon Occupying the right iliac fossa and elevating the iliacus muscle and crural nerves, also extending downward into the pelvis and involving the rectum, is a large mass about 15 cm in diameter The mass extends through the ilium, involved the ischium at the acetabulum, and also the right side of the sacrum On section the tumor tissue is soft, grayish, hemorrhagic, with extensive areas of necrosis There is a separate metastasis in the body of the fifth lumbar vertebra The thyroid area was removed with the tongue The left lobe and isthmus are operatively absent The entire area was now filled with scar tissue and tumor growth The right lobe area contains a tumor mass in which no distinct thyroid tissue is visible The esophagus is free save for very prominent varices in the upper and lower thirds Several small tumor masses project into the lumen of the trachea between the cricoid cartilage and the bifurcation

*Microscopic Examination*—Pancreas and liver normal Spleen Malpighian bodies and pulp cells well preserved Kidney No increase in connective tissue Throughout the cortex are irregular areas of cellular exudate composed for the most part of polymorphonuclear leukocytes In some of the areas the tubules

remained visible while in others actual abscess formation has taken place. Throughout all the acute inflammatory areas the tubules contain pus cells. *Diagnosis:* Acute suppurative nephritis. Heart muscle normal. Lung Congested, moderate coal pigmentation, free from inflammatory exudate.

*Thyroid Area—Right Lobe:* Four sections. No trace of thyroid tissue visible. Extensive areas of tumor cells in the dense stroma. The tumor masses for the most part show no follicle formation. In some, however, slight differentiation but without formation of lumina can be made out. Same irregularities in the cell types as were noted in the operative specimen.

*Lung Metastases:* Slight encapsulation. Central areas necrotic. The cortical zone is divided into small columns and strands of tumor cells by a very delicate vascular stroma. Slight evidence of follicle formation. The inguinal tumor mass also exhibits slight follicle formation. Rib metastasis. Fibrous stroma more prominent and distinct follicle formations can be made out, some of which contain colloid like material. The tissue is distinctly thyroid in type although the cells are as atypical as in other metastases, with less evidence of follicle formation. The bronchial lymph glands contain tumor metastases, the cells of which showed no follicle formation. Tumor from superior vena contain a delicate capillary stroma in places outlining very irregular attempts at follicle formation. The cell types are highly irregular. Nuclear figures are present.

*Anatomical Diagnosis—*Adenocarcinoma of the thyroid, medullary type. Metastases into trachea, the mediastinum, bronchial lymph glands, lungs, ribs, fifth lumbar vertebra and ilium. Acute suppurative nephritis.

Iodin determinations were made on several of the tissues and metastatic tumor nodules obtained at post-mortem as well as on the tumor mass removed at operation.

*Iodin Determinations—*Operative Specimen No. 1. The scar-like tissue corresponding to the thyroid area contains 0.02 mg. per gram of dried tissue.

No. 2—Adenoma freed from all other tissues contains 0.17 mg. per gram of dried tissue.

#### Autopsy Tissues

No. 1—Liver. Iodin per gram dried tissue, 0.00 mg., or a trace.

No. 2—Kidney. Iodin per gram dried tissue, 0.01 mg.

No. 3—Pancreas. Iodin per gram dried tissue, 0.03 mg.

No. 4—Spleen. Iodin per gram dried tissue, 0.00 mg.

No. 5—Lung. Iodin per gram dried tissue, 0.00 or a trace.

No. 6—Lung Metastasis. Iodin per gram dried tissue, 0.00 mg.

No. 7—Rib Metastasis. Iodin per gram dried tissue, 0.00 mg.

No. 8—Iliac Metastasis. Iodin per gram dried tissue, 0.00 mg.

No. 9—Tumor from the site of the right lobe. Iodin per gram of dried tissue, 0.00 mg.

*Iodin Administration:* Nov. 14 to Dec. 8, 1911, syrup of ferrous iodid 34 cc. December 8 to 20, sodium iodid 12 gm. January 8 to April 15, 1912, syrup of ferrous iodid 181 cc. Total iodin before operation, 17 cc. syrup ferrous iodid. Total iodin after operation, 12 gm. of sodium iodid and 198 cc. of syrup ferrous iodid.

*CASE 2—*S. R., City Hospital No. 11,167, admitted Sept. 11, 1911. Female, Hungarian, aged 39. Complaint, cough with loss of weight for the past ten months. Past history not obtained.

*Physical Examination—*Fair development, poorly nourished and cachectic appearance. There is a unilateral tumor mass 5 cm. in diameter in the region of the left lateral lobe of the thyroid. Patient has noticed this enlargement for seven years. Right lobe slightly enlarged but with normal outline. The chest is long and the costal angle narrowed. There is distinct dullness over the right apex and bronchial breathing over both apex and base. Heart, abdomen, and extremities negative. No blood examination. Trace of albumin first noticed December 23, which continued until death. Repeated examinations of the sputum for tubercle

bacilli negative until April 30, 1912, although patient had afternoon temperature of 101 to 102.8 F with pulse averaging 100 to 110

Dec 3, 1911 General condition of patient about the same as at admission. The thyroid tumor had enlarged slightly. It is quite hard and not painful. Displacement of the larynx to which the tumor mass is firmly attached. Skin movable over the tumor. Several isolated nodules are palpable in the left supraclavicular fossa. There is distinct dullness over the left apex of the lung and x-ray plates showed rather dense shadows in both apices.

Dec 12, 1911 Evidence of tracheal stenosis and operation advised.

Dec 20, 1911 The tumor mass was removed.

*Pathological Report*—The mass consists of the left lobe and isthmus. It is firm, nodular, and for the most part encapsulated but in places the tumor tissue extends through. Two of the superficial veins are filled with tumor tissue. On section the tumor mass is whitish, opaque, with a few small necrotic areas. The tumor is sharply defined from the non-tumor thyroid tissue which has all the appearances of normal thyroid tissue. Coarse fibrous strands cut the tumor mass into lobules. In places colloid-like substance is seen.

*Microscopic Examination*—The non-tumor thyroid tissue is uniformly colloid-containing, slightly stretched by the growing tumor but in all respects resembles pure colloid thyroid. The tumor is for the most part undifferentiated into follicles. The interior portion is composed of irregular columns of large cuboidal cells closely set and for the most part without evidence of lumina. There are areas throughout this portion of the tumor in which irregular follicle formations occur. In the peripheral parts of the tumor follicle formation is absent. There is a distinct alveolar arrangement dependent on the stroma. The tumor cells are somewhat irregular, elongated, and with their long axes arranged radially in the alveolus. No adenoma-like areas were made out. Diagnosis, medullary carcinomas.

Dec 24, 1911 Recovery from operation uncomplicated. Temperature 99 to 101 F, pulse 110 to 115. Sodium iodid grains 5, daily. Patient complains of pain in the right hip.

Jan 10, 1912 Cachexia and emaciation not improved, breathing is better. The right leg is swollen and somewhat painful. X-ray at this time shows metastases in the right side of the sacrum.

Feb 27, 1912 Syrup of ferrous iodid minims 10 t i d was substituted for sodium iodid. Flatness over the right chest and the infraclavicular region of the left with dullness beneath the manubrium. No recurrent growth in the thyroid region.

March 20, 1912 Patient's condition progressively downward. Respiration 24 to 28, pulse 110 to 113, temperature 99 to 100. Constant pain in the sacro-iliac region.

April 30, 1912 Sputum contains tubercle bacilli. Transferred to tuberculosis sanitarium and died there May 3, 1912.

*Autopsy*—Autopsy May 5, 1912, after overcoming some difficulties. The body was not embalmed and was in a good state of preservation. Slight discoloration of the abdomen. Examination confined to the chest and abdomen. Thyroid area. Right lobe normal shape, enlarged about twice the normal size. Firm, translucent, and on section contains abundant colloid. A cystic adenoma 2 cm in diameter is imbedded in this lobe. The isthmus was removed at operation. The left lobe for the most part was removed. There is, however, a mass of tissue 4 by 1.5 cm occupying the site of the left lobe, and adherent to the surrounding structures. On examination this mass is found to contain both colloid and cancerous thyroid tissue. The thymus area contains three metastatic tumor nodules, the largest being the size of a golf ball. Both lungs are adherent to the parietal pleura. The right lung contains extensive tuberculous caseation and consolidation. Both lungs contain numerous tumor nodules varying in size from a pea to a golf ball. Heart, small, contains no metastases. Abdomen. Liver contains several metastases, one

large nodular mass just above the gall bladder, measures 6 by 5 by 5 cm. Spleen contains one small tumor nodule. Kidneys both contain metastases. Pancreas contains a metastasis 2 cm in diameter near the duodenum. All metastases observed in the several viscera are grayish opaque in color, soft, friable, and have no gross resemblance to the normal thyroid structure. There are several metastases in the omentum and mesentery. The sacrum contains a large metastasis extending into the pelvis and also producing slight ulceration externally. Stomach and intestines appear normal.

*Microscopic Examination*—Thyroid. Right lobe has all the appearances of pure colloid thyroid. The small adenoma has a subcapsular zone of well preserved, closely set small follicles most of which contain some colloid. Diagnosis. Intermediate adenoma with involutionary changes imbedded in the pure colloid goiter. Three other sections from the right lobe revealed no metastases. Examination of tissue removed from the region of the left lobe shows for the most part dense scar tissue in which are pockets of tumor tissue without any differentiation into follicles. In another section of this mass considerable non-tumor thyroid tissue similar to that of the right lobe is present. Lung metastases encapsulated. They consist of irregular branching columns of tumor cells with slight follicle formations. The cells for the most part are spindle shaped with a tendency toward radial arrangement from the center of the column. In some of the columns lumina are made out. Liver metastases are in all respects similar to those of the lungs. Pancreas metastasis is composed of branching columns of spindle shaped cells. Many of these columns have definite lumina. The pancreatic tissue has undergone extensive post mortem changes. The kidney metastases have a distinct alveolar arrangement of the tumor cells with little or no tendency to form follicles. The surrounding kidney tissue including capsule, glomeruli and tubular epithelium are relatively normal.

*Iodin Determination*—Operative Specimen. No 1—Iodin per gram of dried non-tumor thyroid, 0.80 mg.

No 2—Iodin per gram of dried tumor thyroid, 0.03 mg.

#### Autopsy Tissues

No 1—Right lobe pure colloid gland, iodine per gram of dried gland, 2.92 mg.

No 2—Left lobe, mixed tumor and non-tumor thyroid, iodine per gram of dried gland, 0.16 mg.

No 3—Lung metastasis, iodine per gram of dried gland, 0.00 mg.

No 4—Liver metastasis, iodine per gram of dried gland, 0.00 mg.

No 5—Esophagus tissue, tumor free, iodine per gram of dried tissue, 0.00 mg.

No 6—Pancreas tissue, tumor free, iodine per gram of dried gland, 0.00 mg.

No 7—Liver tissue, tumor free, iodine per gram of dried gland, 0.00 mg.

*Administration of Iodin*—Total iodine before operation, 0.

Total iodine after operation. (a) Dec 24, 1911, to Jan 5, 1912, 1 gm sodium iodid daily, total 13 gm. (b) Feb 27, 1912, to April 25, 1912, 10 minims syrup ferrous iodid t.i.d., total 119 cc.

In addition to these two human cases one of us (M.) has observed a case of thyroid carcinoma in a dog, and inasmuch as the data are in all respects similar to those for the human cases it may also be included here. The following is a synopsis of the case record.

CASE 3—Laboratory No. A-124, male Boston Bull-Terrier, aged 8 years, owned by Dr. E. P. Carter, admitted May 1, 1908.

*History*—Goiter had been known clinically for over three years, with progressive enlargement. First examined dog on Oct. 9, 1907. Thyroid lobes at this time were symmetrically enlarged, compressible, distinct, movable and connected by a broad isthmial band. Diagnosis, active thyroid hyperplasia. Lugol's solution 0.1 cc daily was given. This treatment was continued with very slight interruptions until May 8, 1908. The dog was seen from time to time and the thyroid lobes, which at first became smaller, began to enlarge again in February, 1908. Their

outlines became less distinct. Gradually both lobes and isthmus became fused into a single mass and the entire mass became firmly adherent to the larynx. In April the thyroid mass was more distorted, firm, and immovable, and was producing dyspnea. As the dog was now losing weight and the thyroid lobes had undergone marked changes, the probability of thyroid carcinoma was suggested and operation advised. May 8, 1908, under ether anesthesia the entire left lobe was removed. It was densely adherent to the trachea, larynx, esophagus and adjacent muscles, and weighed 145 gm.

*Pathological Examination*—The lobe was nodular, although everywhere encapsulated. Consistency was firm. On section there were still some very definite areas of original thyroid tissue in the colloid state, for the most part lying just beneath the capsule, but in general the entire lobe was replaced by a new growth. The tumor tissue was grayish opaque in color, containing many small hemorrhages and small areas of necrosis, together with a few cystic areas filled with a brownish cholesterol-containing fluid. It was impossible to separate the tumor from the non-tumor thyroid tissue and duplicate iodine determinations were made on the mixed tissue with results of 0.32 and 0.30 mg per gram of dried gland.

May 11, 1908, dog doing nicely.

May 16, 1908, wound slightly infected, and as the dog had undoubted carcinoma the owner desired him chloroformed.

*Autopsy*—Slight wound infection. The right lobe weighed 125 gm, was nodular, hard, gray-red, and on section was equally involved with cancer as the left lobe, which was removed at operation. Extension of carcinomatous tissue into the anterior mediastinum. Both lungs contained numerous metastatic nodules varying from 1 mm to 2 cm in diameter. They were gray-white, friable, and contained no visible colloid. The lymph-glands along the bronchi were involved. No metastases were found in the kidneys, liver, pancreas, or other viscera. As the dog had been getting iodine up to the time of operation, iodine determinations were made on the autopsy tissues as follows:

Right lobe of the thyroid contained 0.27 mg per gram of dried gland.

Lung metastasis contained 0.11 mg per gram of dried tissue.

Lung tissue contained 0.07 mg per gram of dried tissue.

Liver tissue contained 0.15 mg per gram of dried tissue.

*Histological Examination*—Thyroid. The capsule was markedly thickened. Slight round-celled infiltration. There were many areas of original non-tumor thyroid containing normal colloid and normal cuboidal epithelium. The tumor tissue was in general differentiated into follicles. These were small, rounded, closely packed and resembled the fetal adenoma follicles seen in human goiter. There were other areas or irregular islands making up probably a third of the sectioned area in which little or no differentiation into follicles could be made out. The epithelium of the formed follicles was high cuboidal in type and the nuclei were large vesicular, quite regular in size and staining intensity. Lung Metastases. Six were examined, all showing some differentiation into follicles, of the same characteristics present in the thyroid lobes.

#### SUMMARY AND DISCUSSION

The principle data of Case 1 are: Patient was under observation 168 days—23 days before and 145 days after operative removal of part of the thyroid tumor. Metastases were without doubt present before the patient came under our observation. The thyroid contained several adenomas of the fetal type and while it is impossible to state from what portion of the thyroid the carcinoma originated, we have come to the conclusion from the tumor pattern that it probably originated from an

adenoma The whole course of the disease was, as far as could be determined, one of uncomplicated thyroid cancer Seventeen c c of syrup of ferrous iodid was given before operation and 12 gm of sodium iodid, and 198 c c of the syrup of ferrous iodid were given after operation—iodin having been continuously administered from Nov 14, 1911 to April 15, 1912 with the exception of eighteen days from Dec 20, 1911

Case 2 was in the hospital continuously from Sept 11, 1911, until her death, May 3, 1912—235 days She was admitted for and had active pulmonary tuberculosis Thyroid carcinoma was not definitely recognized until December 3, when, owing to tracheal stenosis, a palliative operation was advised The tuberculosis doubtless hastened death The tumor though metastasizing was of slower growth than that of Case 1 The carcinoma and the tuberculosis were joint factors and the individual importance of each cannot be estimated In this case also there was one typical adenoma in the right lobe and the general type of tumor led us to look on this carcinoma as also originating in an adenoma No iodin was given prior to the operation Following the operation iodin was given continuously until April 25, 1912—eight days before death—with the exception of fifty-two days following Jan 5, 1912 She received a total of 13 gm of sodium iodid and 119 c c of syrup of ferrous iodid

Case 3 (a dog) was under observation for approximately seven months Carcinoma was suspected after the fifth month Small doses of Lugol's solution were administered by mouth with slight interruptions from October until May 8 The total amount of iodin used could not be obtained

The scar-like mass of the left lobe removed at operation in Case 1, after freeing it from all visible adenomatous tissue contained 0.02 mg of iodin per gram of dried tissue The adenoma from the same lobe contained 0.17 mg of iodin per gram of dried tissue The patient had been getting iodin for eleven days before operation Adenomas of histological differentiation present in this case normally contained some iodin, and while the comparatively high content may be explained on the basis of the iodin administered, this does not seem likely, judging from our experience with adenomas in general The iodin content of the scirrhous cancer tissue is, on the other hand, probably due to the administration of iodin, judging by the distribution of iodin in the tissues and its rate of excretion following its administration in dogs and rabbits The iodin contents of the tissues at autopsy, notwithstanding the fact that iodin was given until five days before death, shows no traces of iodin in the remaining scar-like cancerous mass of the right lobe, in the spleen in the rib, lung, or iliac metastases Definite traces of iodin were found in the lung and liver tissues while the kidney and pancreas con-

tained 0.01 and 0.03 mg per gram of dried tissue, respectively. The fact that the pure cancer tissues were free from iodine while the adenomas had over eight times as much iodine as any of the other thyroid tissues and about six times as much as the pancreas, possibly suggests that this was the best preserved thyroid tissue. Certainly the carcinoma tissues showed no power whatever to retain iodine, although the tissues were exposed to the most favorable influences for iodine storage.

In Case 2 the portion of the left lobe removed at operation was separated into tumor and non-tumor tissues. The non-tumor tissue contained 0.80 mg of iodine per gram of dried tissue, while the adjacent tumor tissue contained 0.03 mg of iodine per gram of dried tissue. This specimen looked like pure cancer tissue, and histological examination of several areas of it showed only tumor tissue. No iodine had been administered for nearly three and a half months. The remaining portion of the left lobe obtained at autopsy contained both tumor and non-tumor thyroid tissue, but was so intermingled that no separation was possible. The mixed specimen contained 0.16 mg of iodine per gram of dried tissue. The right lobe, which on gross and histological examination was pure colloid thyroid, contained 2.92 mg of iodine per gram of dried gland, or nearly four times the iodine content of the non-tumor thyroid of the left lobe obtained at operation before iodine was given. In this case neither the metastases in the liver and lung nor the non-tumor liver, kidney, pancreas, lung and esophagus tissues contained any trace of iodine although iodine had been given for a long time and up to eight days before death. This case has the advantage over Case 1 in possessing an abundance of thyroid tissue unaffected by tumor, and it is noted that this tissue reacts with iodine in the characteristically normal physiological manner.

In Case 3 duplicate determinations on the operative specimen showed 0.32 and 0.30 mg of iodine per gram of dried tissue, respectively. The examined specimens were mixed tumor and non-tumor as the tumor growth had so infiltrated the whole lobe that separation was impossible. The observation is therefore useless so far as determining whether the tumor tissue contained iodine. Likewise, the left lobe removed at autopsy was so infiltrated with cancer that separation was impossible and the iodine determination on a mixed specimen gave 0.27. The lung metastases showed 0.11 mg of iodine per gram of dried tissue, while the tumor-free lung and liver—the only other tissues examined—gave 0.07 and 0.15 mg of iodine per gram of dried tissue, respectively. From these findings and from the general distribution of iodine in the body following its administration it is probable that all the tissues contained iodine. The fact that the iodine content of the liver was higher than that of the lung metastasis renders the iodine content of the lung metastasis of no physio-



logical significance, and the iodine content of the lung and liver is probably due to the non-excretion of the recently administered iodine. Whether iodine in the form of Lugol's solution is held by the tissues longer than iodine given as syrup of ferrous iodide is a question barely suggested by the striking difference in the iodine contents between the two human cases and the dog. In most of the work on the retention of iodine in the tissues potassium and sodium iodide have been used, the last traces of which are known to be excreted slowly. The administration of iodine in these three cases had neither a detectable inhibiting influence nor a detectable accelerating influence on the rate of growth.

In these three cases, therefore, it seems that cancer tissue exhibits practically no capacity for iodine retention, contrasted with the non-tumor thyroid, which has a marked capacity for storing iodine, and with benign epithelial tumors (adenomas), all of which in some phase of their existence have some capacity for iodine, thyroid cancer exhibits the least—in our three cases probably no capacity for iodine. We have been able to find but two incomplete reports in the literature of iodine determinations in metastatic thyroid carcinoma. Ewald<sup>8</sup> reported one case in which the examination of the primary tumor (a thyroid adenoma) showed no iodine, while metastases in the lung and lymph-glands showed appreciable amounts. No other details of the case are given. He suggested that further examinations should be made, since if Baumann's observations and conclusions should be established the iodine contents of tumors might afford evidence as to tumor function. Gierke<sup>9</sup> observed a vertebral tumor with thyroid-like structure which contained approximately 0.25 mg of iodine per gram of dried tissue. No other details are given and on this account it is impossible to make comparisons with our tumor cases. As there are more differentiated types of thyroid carcinoma, or possibly more correctly stated, there are metastatic thyroid growths especially in bone which morphologically closely resemble fully differentiated thyroid tissue, the need of more extended observations is obvious, as it might be possible to determine through their iodine function what relation they bear to tumors, since morphology is of little value. As dogs are not known to have adenomas we suppose that the carcinoma in Case 3 arose from tissue that had undergone physiological differentiation. If such was the case the physiological attributes have been lost, as the tumor behaved towards iodine in a similar manner to the two human carcinomas. We have as yet no direct evidence that thyroid tumors, whether benign or malignant, may compensate for the function of the non-tumor thyroid. Experimental approach has so far been impossible because none of the

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8 Ewald Ueber den Jodgehalt des Adenocarcinome der Schilddrüse und seine Metastasen. *Wien klin Wchnschr*, 1896, lx, 186

9 Gierke Ueber den Jodgehalt von Knochentumoren mit Schilddrüsenbau. *Beitr z chem Physiol u Path*, 1903, iii, 286

lower mammals is known to have true adenomas. The often quoted observation of von Eiselsberg<sup>10</sup> to the effect that following the removal of a large goiter tetany developed which cleared up as sternal thyroid metastases developed, was made at a time when parathyroid and thyroid functions were not clearly separated. Such symptoms are not now believed to have connection with thyroid. More applicable are the observations of Gulliver<sup>11</sup> where a woman 44 years old with symptoms of myxedema dating back four years developed thyroid carcinoma with metastases, but without any noteworthy amelioration of the myxedema symptoms. This author also cites an observation reported by Hilton Fagge where a sporadic cretin with a large goiter developed thyroid carcinoma without any improvement in the cretinoid condition. Such clinical observations though meager are in harmony with the experimental chemical evidence of the cases here reported, viz, that in thyroid carcinoma there is no evidence that useful function is preserved, but rather that in becoming malignant the tissue loses most of its physiological attributes. So far as observations have extended, it would appear that benign epithelial tumors occupy an intermediate position as regards evidence of function between fully differentiated thyroid tissue on the one hand and malignant epithelium tumors on the other.

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10 Von Eiselsberg Arch f klin Chir, 1894, xlviii, 489

11 Gulliver Malignant Disease of the Thyroid Developing in a Case of Myxedema Tr Path Soc, London 1886, xxxvii, 511

## CONCERNING THE PRESENCE OF HEMOLYSINS IN STOOL EXTRACTS

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The following experiments were undertaken with the aim of ascertaining, if possible, whether extracts of stools from cases of essential progressive pernicious anemia contain hemolysing substances not found in normal stools, nor in stools from other diseases. If repeatedly present, this could be regarded as of some use as a further step in the clinical diagnosis of a disease the etiology of which is still uncertain and the classification of which is hardly satisfactory.

In reviewing the literature on hemolysins in the gastro-intestinal tract, I find that while much has been done with tumor and organ extracts, little attention has been paid to the stools.

Korschun and Morganroth,<sup>1</sup> in their work on the hemolytic action of organ extracts, describe a hemolysin thus derived, which is active against the blood-cells of the same species and possesses the following characteristics: coetostabile, soluble in alcohol, not complex, and inactive in causing antibody formation.

Later Kulbs,<sup>2</sup> in a series of experiments on stool filtrates, showed the presence of hemolysins in cases of intercurrent and chronic intestinal disorders as well as in progressive pernicious anemia. In chronic nephritis and diabetes agglutinins were frequently encountered. The hemolytic action of the filtrates was not affected by type of diet, heating or age of filtrate, nor did the reaction play any part in the result. He found no relation existing between the indoxyl content of the urine and the hemolytic effect of the stool. The solubility of the stool and apparent quick passage through the bowel seemed to be more important factors. Thin stools taken directly from cecum and ileum were very hemolytic. He does not refer to the chemical constituents. Injections into animals of 2 to 6 c.c. produced no anemia.

In the following year Tallqvist<sup>3</sup> reported his results on the study of the blood changes produced by the *Bothriocephalus latus*, results which

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\*From the Pepper Laboratory of Clinical Medicine, University of Pennsylvania Under the J. Alison Scott Research Fund.

\*Read before the Pathological Society of Philadelphia, Oct. 24, 1912.

1 Korschun and Morganroth. Berl. klin. Wochenschr., 1902, p. 870.

2 Kulbs. Arch. f. exper. Path. u. Pharm., 1906, No. 55, p. 73.

3 Tallqvist. Ztschr. f. klin. Med., 1907, No. 61.

were most striking and of material value in explaining the etiology of such anemias. He demonstrated the presence of a lipid substance in the proglottides of the worm, which was extremely hemolytic, could not be dissected out, formed no antibodies, was coctostabile, resistant to proteolytic ferments and showed a great affinity for red blood-cells. On subcutaneous injections into animals a definite anemia was produced, the autopsy findings being similar to those of a progressive pernicious anemia.

He refers to substances possessing similar hemolysing qualities in normal organ extracts, especially in mucous membranes of certain sections of the gastro-intestinal tract. He suggests that in many cryptogenic forms of progressive pernicious anemia there may be qualitative or quantitative anomalies in fat metabolism calling forth a pathological separation and a consequent hemolytic lipid substance. Such substances have been described in various tumors and secretions. Thus Kullmann<sup>4</sup> found them in mammary and uterine carcinomata. Grafe and Rohmer<sup>5</sup> (whose work was later partially confirmed by Fabian<sup>6</sup>), in a series of over 100 cases, demonstrated hemolyzing lipoids repeatedly in the gastric contents of gastric carcinoma, while Neubeig and Reicher<sup>7</sup> showed that normal neutralized gastric contents of dogs were hemolytic to cells of the same animal. Later Bloch<sup>8</sup> claimed that if the enterogenous theory of progressive pernicious anemia was correct, the toxic agent should be found in the stools. He found hemolytic substances in the stools of six cases of progressive pernicious anemia, in chronic enteritis, (one case), and in tabes, but the most marked hemolysis occurred with normal stools. He concluded that the normally formed lipid in the intestinal contents was rendered inert by cholesterol, and, when this failed, hemolysis occurred. The fact, however, of the strongest hemolysis having occurred in normal stools, in his own experiments, does not satisfactorily support this theory. He used alcoholic and ethereal extracts only. The substance was not activated by lecithin. Wohlgemuth found hemolysins in pancreatic juice, which were activated by lecithin.

Next Faust and Tallqvist,<sup>9</sup> after further studies in the chemistry of *Bothriocephalus* proglottides showed the lipid substance to be soluble in warm alcohol and ether, but not in water, and only capable of producing hemolysis when the sheath was disintegrated. The fatty material contained phosphorus from lecithin. Cholesterol was crystallized out, but was not hemolytic. Free fatty acids were found to be intensely hemo-

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4 Kullmann 'Berl klin Wehnschr, 1904, No 8

5 Grafe and Rohmer, D Arch f klin Med, 1908, No 93, p 159

6 Fabian, D Arch f klin Med, 1908

7 Neubeig and Reicher Biochem Ztschr, 1907, No 4, p 28

8 Bloch Biochem Ztschr, 1908, No 9, p 498

9 Faust and Tallqvist Arch f exper Path u Pharm, 1907, No 57, p 367

lytic, but on further analysis palmitic and stearic acids (saturated) produced no hemolysis, while the unsaturated oleic acid was intensely active. When in combination with a cholesterol ester, it was most effective, although the cholesterol ester of fatty acids is present in most normal blood-serum in small amounts.

Cholesterol in feces is in part enterogenous, while part comes from bile and some from soap in chyle. Faust and Tallqvist hold that stimulation of the intestinal mucous membrane leads to a greater formation and secretion of this substance, and, with it, an increase of soap in chyle and in blood. Thus, through abnormal stimulation of a normal process, blood destruction could be produced.

By feeding *Bothriocephalus* lipid to dogs large amounts of very hemolytic chyle were recovered in a few hours. Chyle showed neutral fat and free fatty acids, the latter being intensely hemolytic, due to oleic acid. No cholesterol was found in chyle.

Goodman and Robinson,<sup>10</sup> in an unpublished work, demonstrated the presence of hemolytic lipid substances in ethereal extracts of stools from anemias and uterine carcinoma as well as in normal stools.

#### TECHNIC

To weighed stool an equal volume of 85 per cent NaCl was added, the mixture ground up in a mortar, filtered through gauze and allowed to extract over night in an ice chest. On the following day the mixture was shaken, centrifuged and the supernatant fluid passed through a Berkefeld filter, the filtrate being used as the extract, 1 cc representing 1 unit. To a series of tubes containing 1 cc of a 5 per cent emulsion of washed red blood cells from the patient whose stool was being examined, was added a varying amount of the stool extract, from 2 cc down to 1 cc. Sufficient physiological salt solution was added so that the mixture in each tube was brought up to 3 cc. Similar amounts of the stool extract were added to a 5 per cent emulsion of foreign human washed red blood cells. The protocol is as follows:

#### PROTOCOL OF EXPERIMENT WITH STOOL EXTRACT

Diagnosis	Amount of Stool Extr 1 cc = 1 Unit cc	5 Per cent Emulsion R B C of Same Case, cc	5 Per cent Emulsion Foreign R B C of Normal Resistance, cc	Hemolysis
	20	1	—	
	10	1	—	
	05	1	—	
	01	1	—	
	20	—	1	
	10	—	1	
	05	—	1	
	01	—	1	

<sup>10</sup> Goodman and Robinson Unpublished work

## Case

Gastric—		
1	Hyperchlorhydria and dilatation	Positive-Negative
2-6	Neurosis (5 cases in all)	Negative
7	Carcinoma	Negative-Positive
8-9	Toxic gastritis (?) (2 cases)	Negative
10	Chr gastritis (2 times)	Positive
11	Gastroptosis and enteroptosis	Positive
12	Undiagnosed	Positive
13	Undiagnosed	Negative
Intestinal—		
14-15	Chr constipation (2 cases)	Negative
16	Chr appendicitis, <i>Ascaris lumbricoides</i> , and trichocephaliasis	Positive
17	Neoplasm of jejunum	Negative
Kidney—		
18	Uremia	Positive
19	Amyloid nephritis	Positive-Negative
20	Renal calculus and erysipelas	Positive
21	Acute parenchymatous nephritis	Positive
22	Acute parenchymatous nephritis	Negative
23-25	Chr parenchymatous nephritis (3 cases)	Negative
26	Chr parenchymatous nephritis with chorea	Positive-Negative
27	Chr parenchymatous nephritis	Positive-Negative
Metabolic—		
28 33	Diabetes (6 cases of varying severity)	Negative in all
34	Gall-stones	Positive
35	Arthritis, neisserian	Negative
36	Arthritis deformans	Positive
37	Chr family jaundice	Positive-Negative
38	Chr family jaundice	Strong
39	Chr family jaundice	Negative
40	Hepatic cirrhosis	Strong
41	Multiple serositis	Negative
Blood—		
42-45	Progressive pernicious anemia (4 cases)	Negative
46	Progressive pernicious anemia	Very faint negative
47	Progressive pernicious anemia	Positive
48	Lymphatic leukemia	Positive
49	Myelogenous leukemia	Negative
50	Splenomegaly	Positive
Heart—		
51-52	Myocarditis (2 cases)	Negative
53	Chr in myocarditis	Negative
54	Chr in myocarditis	Negative
55	Mitral regurgitation	Negative
56 66	Normal cases (11 stools from 3 cases)	All Negative

## NOTES OF CASES

CASE 1—Hypertrophy and dilatation of stomach This was positive to blood of that case while it did not hemolyze foreign blood-cells

CASE 7—Gastric carcinoma was at first negative, but a few days later proved to be positive

CASE 19—Amyloid nephritis This was positive at first but later negative as were Cases 26 and 27, both chronic nephritis

CASE 38—Chronic family jaundice This was at first strongly hemolytic and later negative while Case 40, hepatic cirrhosis, was strong but not complete

CASE 47—Progressive pernicious anemia This was complete with same cells but only very slight with normal foreign cells

To avoid any influence that might be brought about by the increased fragility of individual cases, red blood-cells from a normal case, that is, red blood-cells capable of resisting hemolysis in hypotonic salt solutions down to 44 per cent NaCl, were used.

It will be observed from the above table that normal stools repeatedly, and stools from progressive pernicious anemia and gastro-intestinal diseases frequently, were negative, and that the results are not analogous to those of Kulbs, whose procedure was quite similar to the above. Nor is there any analogy to the results of Bloch, who, in his series of ten cases, used an ethereal and not a salt solution extract.

The properties of the filtrates were as follows. Light to dark brown, of fecal odor and of variable reaction, the latter playing no part in the hemolytic action of the stool. Nor was there any association between the type of food or use of purgatives and hemolysis. No acholic stools were examined. The presence of indoxyl in the urine, and of the phenol and amido groups in the filtrates had no relation to hemolysis, nor did the action of heat (58 C for one hour) play any part. On prolonged standing the action became weakened and finally lost after seven days.

Fatty acids and neutral fats were present alike in active and inactive stools, as were precipitations of phosphates occasionally.

The results were so inconstant in my series of cases that I feel that no dependence should rest on this test, either as an aid to clinical diagnosis or as a means of enlightenment etiologically.

In conclusion I wish to extend my thanks to Dr. Stengel for the suggestion of this work and the use of the patients in his wards in the University hospital as well as to Drs. E. H. Goodman and Herbert Fox for their kind assistance.

# EXPERIMENTAL OBSERVATIONS ON THE COAGULATION OF OXALATED PLASMA, WITH A STUDY OF SOME CASES OF PURPURA \*

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Stimulated by Whipple's<sup>1</sup> study of the blood-plasma of purpura, and also by the availability of a few patients with purpuric manifestations, we undertook the study, from the point of view of clinical adaptability, of the methods of determining the coagulation properties of the blood-plasma of purpura. We found it necessary, however, in connection with this work, to study in detail the general principles of coagulation, and we therefore present our results under the two general heads of (1) "Experimental" and (2) "Clinical Studies."

## EXPERIMENTAL STUDIES

In the course of our early work we were impressed with the ease of preparing from dog's blood-cells a solution with great thromboplastic activity and comparatively so free from prothrombin or thrombin as to be available as a source of thromboplastin in clinical studies. This solution was prepared as follows. From a normal dog that had fasted twenty-four hours, blood from the jugular vein was allowed to flow into a 1 per cent sodium oxalate solution in the proportion of nine parts of the former to one of the latter, which was immediately centrifugalized. The clear plasma was drawn off and preserved, the cells were washed three times with 0.85 per cent sodium chlorid solution and then diluted with three volumes of distilled water. When hemolysis had occurred, 0.85 gram of sodium chlorid was added for each 100 c c of distilled water. This is quite similar to the solution of platelets prepared by Bayne-Jones, we have not, however, for our purposes found any advantage in isolating the platelets in pure form.

To determine whether this solution contained any considerable amount of thrombin or available prothrombin it was mixed with a solu-

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<sup>1</sup>From the medical wards of the University Hospital and the John Herr Musser Department of Research Medicine, University of Pennsylvania.

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<sup>1</sup> Whipple, G. H. Hemorrhagic Disease. THE ARCHIVES INT. MED., 1912, ix, 365.



tion of pure fibrinogen prepared according to Howell's<sup>2</sup> method, except that dog's plasma was used instead of cat's plasma, as follows 0.5 c c fibrinogen solution + 0.5 c c blood-cell solution + 0.3 c c CaCl<sub>2</sub> solution (2 per cent) No clotting occurred in an hour, thus proving this solution to be free from thrombin or uncombined prothrombin

To determine coagulation time the mixture to be tested was placed in a small test-tube and mixed by shaking Once every half minute, from the time the calcium was added, a platinum loop was dipped into the mixture and the beginning of coagulation was arbitrarily fixed as the time when first a strand of fibrin could be drawn out of the fluid by the platinum loop The platinum loop was then laid aside and once a minute the test-tube was tilted until it could be turned upside down without change of position of the clot, the time when this was possible was taken as the time of complete coagulation This was the routine procedure in all experiments

To determine whether the blood-cell solution contained any fibrinogen it was tested with a solution containing thrombin, obtained as follows To 1 c c of dog's oxalated plasma was added 0.3 c c of calcium solution When clotting was entirely completed the clot was removed and the fluid pressed from it The resulting clear serum remained free from clot for an hour, but when added to fibrinogen solution clotting occurred This serum was added with calcium to the blood-cell solution, as follows 0.5 c c blood-cell solution + 0.5 c c serum + 0.3 c c calcium solution No clotting occurred in an hour, proving the blood-cell solution to be free from fibrinogen

*That this solution shows the properties of Howell's thromboplastin* is clearly demonstrated in the accompanying experiment (Table 1) with dog's oxalated plasma (D<sub>2</sub>), which, on standing in the ice-chest for a few days, had lost some of its original activity

TABLE 1—EXPERIMENT DEMONSTRATING ACTION UPON DOG'S PLASMA

Plasma D. c c	Blood Cell Solution c c	Calcium Solution, c c	Begins, Minutes	Complete, Minutes
0.5		0.15	7	15
0.375	0.125	0.15	1¾	3
0.25	0.25	0.15	1½	2
0.125	0.375	0.15	1	1½
	0.5	0.15	,	

\*None in 1 hour

Further experiments with this blood-cell solution follow

On removing the clot that had formed after adding calcium to plasma D<sub>2</sub>, a serum was left which would not cause the clotting of a

2 Howell, W. H. The Preparation and Properties of Thrombin, Together with Observations on Antithrombin and Prothrombin. *Am Jour Physiol*, 1910, **xxvi**, 453.

solution of fibrinogen. On the subsequent addition, however, of the blood-cell solution clotting was prompt, for example

0.5 cc fibrinogen solution + 0.5 cc serum D<sub>2</sub> + 0.3 cc calcium, no clotting in seventeen minutes

On adding 0.5 cc blood-cell solution Clotting begins, three minutes, complete, four and one-half minutes

This experiment was repeated with a slight variation as follows

0.5 cc fibrinogen solution + 0.5 cc blood-cell solution + 0.3 cc calcium, no clotting in eighteen minutes

On adding 0.5 cc serum D<sub>2</sub> clotting begins, two minutes, complete, four minutes

A slightly different result was obtained when the blood-cell solution and serum D<sub>2</sub> and calcium were allowed to stand together with the subsequent addition of fibrinogen solution, thus

0.5 cc blood-cell solution + 0.5 cc serum D<sub>2</sub> + 0.3 cc calcium

No clotting in fourteen minutes. On then adding 0.5 cc fibrinogen solution a small distinct clot formed after 18 minutes, but never clotted solidly

It is evident that clotting occurred only when all four solutions were combined, the fibrinogen, the serum, the blood-cell solution and calcium, no three of these sufficed to produce coagulation

The explanation which we offer for these experiments is based on Howell's theory. On standing in the cold the prothrombin of plasma D<sub>2</sub> was to a considerable extent bound by antithrombin, causing a delayed clotting time. On the addition of blood-cell solution, however, the prothrombin-antithrombin combination was broken up and prothrombin rendered available. In the serum left after clotting plasma D<sub>2</sub>, all the prothrombin is apparently combined with antithrombin and is inactive until set free by the addition of the blood-cell solution.

With a view to determining the source of this thromboplastin in the blood-cell solution, the blood-cells of oxalated plasma were centrifuged. White blood-cells from the upper layer were collected and after repeated washing treated with three volumes of distilled water. Erythrocytes from the bottom of the centrifuge tube were collected separately, and after washing, were hemolyzed in three volumes of distilled water. The remaining cells of the middle layer were then mixed and similarly washed and hemolyzed. These three solutions so obtained were then tested in ascending dilutions for their power of accelerating the coagulation of a dog's oxalated plasma. This power was found to disappear in each of the three solutions at approximately the same dilution. The thromboplastin was not, therefore, derived exclusively from the leukocytes, nor erythrocytes, but can be obtained, as also shown by Howell<sup>3</sup> and by

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<sup>3</sup> Howell, W. H. The Nature and Action of the Thromboplastic Substance of the Tissues. *Am Jour Physiol*, 1912, **xxxi**, 1

Bayne-Jones,<sup>4</sup> from any of the blood-cells, but particularly from the blood-platelets

For our purpose, the study of clinical cases, this solution of thromboplastin is to be preferred to the commonly-used tissue extracts, because of its greater ease of preparation and its greater activity

To determine whether the destruction of prothrombin or its fixation by antithrombin could be hastened by exposure of the dog's oxalated plasma to heat, the plasma was kept at 47 C for half an hour. This usually retarded coagulation (see Table 2), but the effect varied in different plasmas

TABLE 2 — RETARDATION OF COAGULATION BY SUBJECTING DOG'S OXALATED PLASMA TO HEAT

Plasma D <sub>s</sub> , c c.	CaCl <sub>2</sub> , c c	Clotting	
		Begins, Minutes	Complete, Minutes
1	0.3	3	5
1*	0.3	1	6
1†	0.3	9	18

\*After heating to 47 C for 15 minutes

†After heating to 47 C for 30 minutes

If, however, such a heated plasma was allowed to stand at room-temperature for twenty-four hours, clotting either did not occur on the addition of calcium solution, or was very much delayed (see Table 3 [3]). The thromboplastin solution, however, still exerted a markedly accelerating effect on the coagulation of such heated plasma (see Table 3 [4]) and restored the coagulation time to a point close to that found before heating (see Table 3 [1 and 2]).

TABLE 3 — RETARDATION OF CLOTTING OF HEATED PLASMA AFTER STANDING FOR TWENTY-FOUR HOURS

	Plasma D <sub>s</sub> , c c	CaCl <sub>2</sub> , c c	Thromboplastin Solution, c c	Clotting	
				Begins, Minutes	Complete, Minutes
1	1	0.3		2	4½
2	0.75	0.3	0.25	1½	2
3	1*	0.3		†	
4	0.75*	0.3	0.25	2½	3

\*Plasma D<sub>s</sub> heated at 47 C for one hour and kept at room temperature 24 hours. †No clot in 30 minutes

The addition of one drop of thromboplastin to Tube 3 after it had stood for thirty minutes with no clotting, caused clotting to commence in two and one-half minutes, complete clotting occurred in five minutes. It would appear that the higher the temperature at which the oxalated plasma is allowed to stand, up to 58 C, the more rapid and the more

4 Bayne Jones, S. The Presence of Prothrombin and Thromboplastin in the Blood Platelets. *Am Jour Physiol*, 1912, xxv, 74

complete is the disappearance or fixation of its available prothrombin. An abundance of prothrombin is, however, rendered available again on addition of a thromboplastin solution. In this connection it is of interest to note that Blaizot<sup>5</sup> has shown that an antithrombin develops in dog's oxalated plasma on standing in the cold.

#### INFLUENCE OF HEMOGLOBIN IN THE PLASMA ON THE ESTIMATION OF FIBRINOGEN

The observation that when the thromboplastin solution is heated to 58 to 60 C, a marked precipitation occurs, called attention to a possible occasional source of error in the estimation of fibrinogen by Whipple's method.<sup>1</sup> The following experiment in which a blood-cell solution and oxalated plasma have each been treated as in Whipple's method illustrates this.

Five c c of the thromboplastin solution were placed in a graduated centrifuge tube. A like quantity of a dog's clear oxalated plasma was placed in a similar tube. Both tubes were kept in a water-bath at 58 to 60 C for fifteen minutes and then centrifuged for twenty-five minutes. In the tube containing the plasma was found a sediment of 0.2 c c of coagulated fibrinogen, in the tube containing the hemolyzed blood-cells, a sediment of 1.8 c c. We have already seen that the blood-cell solution is quite free from fibrinogen (see above). It is evident, therefore, that proteins other than fibrinogen, which are coagulated at 58 to 60 C, are liberated from the blood cells on laking. The estimation of fibrinogen by heating to this temperature, therefore, becomes inaccurate if the plasma shows the least evidence of being tinged with hemoglobin.

#### CLINICAL STUDIES

In the clinical study of coagulation we believe that advantage can be taken of the thromboplastin solution described above for demonstrating the presence of prothrombin combined with antithrombin, and that this is an excellent method for detecting an increase in the antithrombin of the blood.

For the clinical study of coagulation we would, therefore, suggest the following steps in addition to a complete blood count and a careful enumeration of the blood-platelets:<sup>6</sup>

- 1 Estimation of the coagulation time of a drop of blood from the finger with one of the clinical coagulometers.
- 2 Take 20 c c of blood from a vein of the arm and mix with 2 c c of 1 per cent sodium oxalate solution and centrifugalize.

<sup>5</sup> Blaizot, L. Extractions de substances anticoagulants du plasma normal de chien. *Compt. rend. Soc. de Biol.*, 1911, lxx, 560.

<sup>6</sup> Duke, W. W. The Pathogenesis of Purpura Hemorrhagica with Especial Reference to the Part Played by the Blood-Platelets. *THE ARCHIVES INT. MED.*, 1912, x, 445.

- (a) To 1 cc of plasma so obtained add 0.3 cc of a 2 per cent calcium chlorid solution and determine beginning and complete clotting *If delayed,*
- (b) To 0.75 cc of the original plasma add 0.25 cc of blood cell solution prepared as described, and 0.3 cc of 2 per cent calcium chlorid, and determine beginning and complete clotting *If delayed,*
- (c) To 0.5 cc of plasma add 0.5 cc pure fibrinogen solution and 0.3 cc of 2 per cent calcium chlorid solution and determine beginning and complete clotting

A delay in (1) but not in (2-a) suggests that there is not sufficient calcium available in the blood for normal coagulation, but that the other constituents are normal, a delay in (2-a) but not in (2-b) suggests that much of the prothrombin present is bound by antithrombin and is therefore inactive. A poor coagulation in (1), (2-a) and (2-b) but good in (2-c) suggests that there is a deficiency of fibrinogen which can be further confirmed at (3) (see below)

A delay in (1), (2-a), (2-b) and (2-c) suggests a deficiency of prothrombin, bound or unbound, with or without a deficiency of fibrinogen

3. Precipitate fibrinogen in 10 cc of plasma by heating to 58 to 60 C for 15 minutes on a water bath. Centrifugalize in a graduated tube for 25 minutes and read amount of sediment in volume per cent. This method is useless if plasma is discolored with hemoglobin (see above)

It may be noted here that a poor filmy clot may result quite as readily from a lack of thrombin as from a lack of fibrinogen in spite of statements in the literature to the contrary. We have repeatedly observed this type of clot in working with solutions of pure fibrinogen in abundance, but containing only a trace of thrombin.

This is shown by the following experiment

Plasma D<sub>2</sub> was clotted in the usual manner and the serum was expressed from the clot. On the addition of fibrinogen to the serum another clot formed and serum was again expressed, this was repeated several times, the clot becoming poorer and smaller each time. An excess of calcium was constantly maintained. The addition of fibrinogen solution to the expressed serum finally resulted in merely a few threads of clot after thirty minutes, due to the exhaustion of the thrombin.

#### CLINICAL CASES

Of the twelve patients whom we have studied clinically, five showed purpura, one jaundice and one severe anemia, the other five were controls of various kinds. The five patients showing purpura were of various types. Our studies of three will be described in detail.

The first is a woman, aged 24, who throughout her life had been subject to subcutaneous hemorrhagic extravasations. These had not disturbed her until the previous five years, during which time the appearance of the extravasations had been preceded by pain, usually localized to that portion of the body where the purpuric manifestations later appeared. Her general health had not been affected. She gave the interesting history that three sisters, her mother and a maternal aunt have all presented similar purpuric lesions, only the aunt, however, suffered pain at the time of the attacks.

The examination of the patient's blood showed Hemoglobin, 69 per cent, red blood-cells, 4,580,000, leukocytes, 8,400 Differential count Polymorphonuclears, 57 per cent, small lymphocytes, 36 per cent, large mononuclears, 2 per cent, transitionals, 1 per cent, eosinophils, 2 per cent, basophils, 2 per cent Blood platelets (preserved by formaldehyd solution) 215,300 per cmm Fragility of erythrocytes in hypotonic sodium chlorid solution

	NaCl Solution—Per Cent			
	0 3	0 35	0 4	0 45
Reading after 1 hour	+	±	±	—
Reading after 24 hours	+	+	±	—

Coagulation of blood Bogg's coagulometer, eight minutes (average of three readings) Wassermann reaction, negative (examination by Dr John Laird)

#### STUDY OF OXALATED PLASMA

Coagulation time was as follows 1 cc plasma + calcium 0.3 cc, clotting began in sixteen minutes, complete in twenty-seven minutes The influence of thromboplastin was shown as follows 0.75 cc plasma + thromboplastin solution 0.25 cc + calcium 0.3 cc, clotting began in four minutes, complete in ten and one-half minutes Equal parts of this plasma and of normal dog's plasma clotted as promptly as the dog's plasma alone Fibrinogen content was 3 per cent by volume

At a later examination, after a month's interval, similar results were obtained The red blood-cell count was 4,520,000, the platelets, 226,000 Coagulation of the blood Bogg's coagulometer, 6 minutes

#### STUDY OF OXALATED PLASMA ON SECOND TEST

Coagulation time was as follows 1 cc plasma + calcium 0.3 cc, clotting of her oxalated plasma, which delay entirely disappeared on addition of thromboplastin was as follows 0.5 cc plasma + 0.5 cc thromboplastin solution + calcium 0.3 cc, clotting began in four minutes, complete in nine minutes

This patient showed, therefore, at two examinations a delay in coagulation of her oxalated plasma, which delay entirely disappeared upon addition of thromboplastin We are inclined to believe, therefore, that her plasma had an excess of antithrombin

Another patient with simple purpura was a girl of 24 whose history was negative previous to two years before admission At that time purpuric manifestations appeared and have continued to be present almost constantly since Her symptoms consisted of hematemesis, epistaxis, bleeding from the gums, marked subcutaneous petechiae and furunculosis A slight tendency to prolonged bleeding from cuts had been noticed This did not begin, however, in childhood and no family history of hemophilia was obtained Physical examination was negative except for the signs of severe anemia Examination of the blood gave the results shown in Tables 4, 5 and 6

TABLE 4—BLOOD-ANALYSIS IN A CASE OF PURPURA HEMORRHAGICA

Date	Hgb, Per cent	R B C	W B C	Poly Per cent	Lymph Per cent	Mono Per cent	Trans Per cent	Eosin Per cent	Myel Per cent	Baso Per cent
5/31/12	20	3,000,000	7,680	74	20	5	1	—	—	—
6/ 3/12	—	—	—	65	27	5	1	1	1	—
6/ 8/12	25	2,500,000	7,040	59	36	3	1	—	—	1
6/15/12	30	3,160,000	—	—	—	—	—	—	—	—
7/ 8/12	50	4,170,000	—	—	—	—	—	—	—	—
7/18/12	60	4,240,000	6,900	—	—	—	—	—	—	—
7/24/12	65	4,950,000	8,100	—	—	—	—	—	—	—
8/ 4/12	75	4,270,000	9,300	80	17	1	2	—	—	—
8/26/12	67	3,700,000	6,100	82	15	1	—	—	—	2

Platelets—6/25/12, 67,000, 7/29/12, 28,500, 8/30/12, 25,000

TABLE 5—FRAGILITY OF RED CELLS

NaCl, Per Cent	Reading* After 2 Hours	Reading After 24 Hours	Reading† After ½ Hour	Reading† After 24 Hours
0.2	100	100	100	100
0.3	100	100	100	100
0.325	+++	100		
0.35	++	+++	++	++
0.375	++	++	t <sub>1</sub>	tr
0.4	++	++	t <sub>1</sub>	t <sub>1</sub>
0.425	+	+		
0.45	+	+	0	0
0.475	t <sub>1</sub>	tr		
0.5	ft t <sub>1</sub>	ft t <sub>1</sub>	0	0
0.525	0	ft t <sub>1</sub>		
0.55	0	ft tr	0	0
0.6	0	ft t <sub>1</sub>		
6/18/12	78/8/12			

Wassermann Reaction Negative (Dr Laird)

Blood Culture *Mycobacterium Hoffmanni* (Examination by Dr Herbert Fox)

Coagulation of Blood Using the Biffi Brooks instrument, coagulation was found to commence in six minutes and to be completed in twelve minutes

Coagulation of oxalated plasma, as determined by a number of readings, was between four and one half and six minutes for the beginning and nine and one-half and twelve for the complete clotting. This is within normal limits.

This plasma, as tested on June 15, 1912, had no influence on the clotting of normal dog's plasma (see Table 6)

TABLE 6—EFFECT OF PLASMA FROM PURPURIC PATIENT ON COAGULATION OF DOG'S PLASMA

Plasma B, c c	Plasma Dog, c c	CaCl <sub>2</sub> , 2% c c	Begin Minutes	Complete, Minutes
—	1	0.3	3	6½
0.05	0.95	0.3	3	5½
0.25	0.75	0.3	3	5½
0.5	0.5	0.3	3	6
0.75	0.25	0.3	4	9½
0.95	0.05	0.3	4¾	11½
1	—	0.3	4¼	9½

The fibrinogen content of the slightly hemoglobin stained plasma was found to be a little less than 10 per cent by volume, but this high reading was doubtless due to contamination of the plasma with products of hemolysis.

Everything is normal in this case except the severe secondary anemia and the marked reduction of platelets. We have normal coagulation, which is the usual finding in purpura, and indeed it may truly be said that the factor determining purpura is not constantly involved in coagulation as studied in oxalated plasma.

Very similar findings were shown in a patient with hemophilia, a woman aged 30, who was admitted suffering from persistent, profuse metrorrhagia with a resulting anemia. A history of hemophilia in the patient and the patient's father was obtained. This transmission of hemophilia from father to daughter, with appearance of symptoms in the daughter, while not the usual history, has been observed. The blood showed

Aug 10, 1912 Hgb, 37 per cent, R B C, 2,140,000, W B C, 11,700, Poly, 87 per cent, Lymph, 11 per cent, Mono, 2 per cent, Trans, —, Eosin, —

Aug 16, 1912 Hgb, 38 per cent, R B C, 2,430,000, W B C, 12,100, Poly, 79 per cent, Lymph, 14 per cent, Mono, —, Trans, 6 per cent, Eosin, 1 per cent

Morphology, normal, no nucleated forms of erythrocytes. Platelets, 37,000

Fragility NaCl per cent	0.25	0.3	0.35	0.4	0.45
Reading after 20 min	+	+	±	±	—
Reading after 24 hours	+	+	±	±	—

Coagulation of the blood measured with the Biffi Brooks coagulometer, beginning coagulation in eight, and complete coagulation in fifteen minutes.

Here again a normal coagulation time was seen in the presence of a reduced platelet count.

Among the cases observed was one of cholelithiasis with intense jaundice over a month's duration. The blood-count was normal.

Hgb, 70 per cent, R B C, 4,000,000, W B C, 5,300, differential Polys 1 per cent, Lymph, 27 per cent, Mono, 5 per cent, Trans, 2 per cent, Eos, 1 per cent, Baso, 1 per cent.

The clotting time of the blood of this case was moderately delayed as estimated with the Biffi-Brooks instrument, clotting commencing but little before fifteen minutes. On the other hand, the oxalated plasma, on the addition of an excess of calcium chlorid, clotted unusually rapidly in two and one-half minutes. In this case the delayed coagulation time as measured in the whole blood was unquestionably due to the union of the calcium of the blood with bile pigments. Pure bile added to normal plasma *in vitro* does not delay the time of coagulation in the presence of an excess of freshly added calcium solution, but, on the contrary, slightly accelerates it as do many foreign solutions. The following protocol is illustrative.

Plasma D <sub>3</sub> , c c	Bile Solution, c c	CaCl <sub>2</sub> , 2% c c	Begin, Minutes	Complete Minute
1	—	0.6	3	4½
0.95	0.05	0.6	1½	2
0.75	0.25	0.6	2	3
0.5	0.5	0.6	2	15

In lower dilutions no clotting occurred. If, however, the solution of bile was allowed to act for ten minutes on the calcium solution before the resulting mixture is added to the plasma, there is very distinct delay of complete coagulation. Such a clot as is found is poor and filmy.

#### CONCLUSIONS

1. A solution of hemolyzed blood-cells is the most readily prepared and active thromboplastic solution.

2. A delay in coagulation time of oxalated plasmas occurs on heating or standing. This is due to the formation of antithrombin, and to the union of antithrombin with prothrombin. The coagulation time in such plasmas is greatly hastened by the addition of thromboplastin solution.

3. The presence of hemoglobin in a plasma is a source of error in the determination of fibrinogen by Whipple's method.

4. The scheme presented for the study of clinical cases is easily carried out and covers the essential points included in the present knowledge of this subject.

5. No method of study has as yet offered a satisfactory explanation of purpura.



# PRIMARY CARCINOMA OF THE LARGER BRONCHI

AN ANALYSIS OF NINETY CASES WITH REGARD TO PATHOLOGY, SYMPTOMATOLOGY AND DIAGNOSIS, AND REPORT OF A NEW CASE

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The large number of case reports of lung and bronchial neoplasms which have appeared in the literature in the last two years gives evidence of a renewed interest in this subject. Two factors have served to draw attention to its importance. There has been a growing realization of the fact that bronchial and pulmonary carcinomata are by no means as rare as was once thought, and the developing possibilities of intrathoracic surgery have made their early diagnosis a matter of more than scientific curiosity. It is hoped that the analysis of a large number of carefully selected cases of primary carcinoma of the larger bronchi will aid in forming a definite clinical picture for this condition and in taking it out of the mixed group of lung and bronchial neoplasms in which it has usually been considered. Even Adler<sup>1</sup> who has written the most extensive of the recent monographs on the subject, does not attempt to separate the two types in his list of cases.

Several attempts have been made to collect from the literature the cases of primary carcinoma of the lungs and bronchi. Reinhard<sup>2</sup> found 25 cases in 1878, Wolf<sup>3</sup> 31 cases in 1895 and Adler<sup>1</sup> 374 cases in 1911. These authors, however, admitted to their lists cases without microscopical verification of their carcinomatous nature. In 1891, Werner<sup>4</sup> could find but nine cases fully verified, while in 1896 Passler<sup>5</sup> listed about 70 such. In differentiating between carcinoma and sarcoma, in ruling out tuberculous processes, and especially in examining metastases and considering the possibility of a primary growth elsewhere, microscopical examinations become necessary, and a statistical study loses in value in proportion as it includes unverified cases.

Wolf<sup>2</sup> separated the cases which he listed into those primary in the lung parenchyma and those having their origin from the larger bronchi.

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<sup>1</sup>Manuscript submitted for publication in THE ARCHIVES Jan. 21, 1913.

<sup>2</sup>From the Pathological Laboratory of the University of Michigan, Ann Arbor, Michigan.

1 Adler, J. Primary Malignant Growths of the Lungs and Bronchi, 1911.

2 Reinhard W. Arch. d. Heilk., 1878, vii, 369.

3 Wolf, K. Fortschr. d. Med., Berlin 1895, viii, 725.

4 Werner, M. Das primäre Lungencarcinom. Dissert., Freiburg, 1891.

5 Passler H. Arch. f. path. Anat., Berlin, 1896, cxlv, 191.

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He placed twenty-three of his thirty-one cases in the second group. It is often found impossible to determine even roughly the point of origin of the growth, because of the enormous size of the neoplasm and the widespread involvement of surrounding structures, but there is a small group in which the bronchial origin may be established. Obvious symptoms and symptomatology of these cases differs very much from that of the group in which the neoplasm is located in the peripheral portions of the lung tree. This difference has been referred to by Passler,<sup>5</sup> but he has not grouped the cases accordingly in compiling his clinical statistics.



Fig 1—Right lung showing right main bronchus (Br) cut across and much reduced by the surrounding carcinomatous infiltration

It is the purpose of this study to collect the authenticated primary carcinoma of the larger bronchi and investigate the pathologic and clinical features of this group. Only those cases meeting the following requirements have been admitted:

1. An autopsy must have been performed
2. The carcinomatous nature must have been verified microscopically
3. There must be no reasonable suspicion that the neoplasm is a secondary growth

4 There must be good evidence of bronchial origin. This may be found either in the gross relationship of the tumor to a bronchus or in the microscopical relationship of the neoplasm to bronchial elements.

As far as possible the following list has been made to include all cases meeting the above tests. The original reports have been used wherever access could be had to them, but full acknowledgment is made of data from Adler's recent monograph<sup>1</sup> in regard to twenty cases in which the original sources were not obtainable. It has also been possible to include nineteen cases which are not found in his somewhat earlier compilation. Beyond a doubt there are many other cases of bronchial carcinoma in the literature, but they cannot find a place here because they fail to meet one or more of the criteria previously mentioned.

#### SYNOPSIS OF REPORTED CASES

1 ALLAN<sup>6</sup> 1907, M, 38. Pain in left chest and arm, dyspnea, palpable tumor at origin of left sternoma-stoid, left pupil contracted, ptosis of left lid, left vocal cord fixed in cadaveric position. Left main bronchus blocked by encircling tumor mass of scirrhous type, with large masses of cells, metastases in bronchial nodes and left lobe of thyroid.

2 BECK<sup>7</sup> 1884 M, 65. Blacksmith. Alveolar carcinoma of right main bronchus and its branches. Lumina constricted, cavity in right upper lobe, secondaries in right bronchial nodes, mediastinal pleura, thyroid, liver, both adrenals, superior vena cava involved and thrombosed, origin from mucous glands.

3 BECK<sup>7</sup> 1884 F, 57. Chairwoman. Primary alveolar carcinoma of right main bronchus and its chief branches, polyhedral cells, bronchial nodes at hilus secondarily involved, stenosis of superior vena cava, origin from bronchial mucous glands.

4 BOECKER<sup>8</sup> 1910, F, 83, housewife. Tumor mass reaching from hilus to pleura in right lower lobe, situated about two medium sized bronchi, alveolar in structure with mucus formation, secondaries in tracheal and cervical nodes (?) not microscopically examined.

5 BOYD<sup>9</sup> 1887 M, 38. Bottle blower. Cough, dyspnea, cyanosis, blood tinged sputum, veins of forehead and neck dilated, edema of right arm and face, voice hoarse and aphonic, carcinoma extending to the right from region of bifurcation and compressing vena cava.

6 DELORME<sup>10</sup> (After Adler) 1901, M, 25. Cough, fever, blood tinged sputum, dilated veins, paralytic symptoms, secondary nodules, cylindric celled carcinoma of left chief bronchus, secondaries in pericardium, pleura, skull, suprarenals, liver, various long bones, sternum, ribs and lymph-nodes.

7 DAVIS AND LE COUNT<sup>11</sup> 1908 M 58. Saloonkeeper. Cough, blood streaked sputum, glandular masses in neck and axilla, dulness and increased fremitus over upper left, hoarseness, dyspnea, cyanosis, paralysis of left vocal cord, carcinoma of left main bronchus, in part adenomatous with mucin like content, origin from mucous glands.

6 Allan, G. A. Lancet, London, 1907, II, 961.

7 Beck. Ztschr. f. Heilk., 1884, v.

8 Boecker, E. Zur Kenntniss der primären Lungenkarzinome. Inaug. Dissert., Berlin, 1910.

9 Boyd. Lancet, London, 1887, II, 60.

10 Delorme. Ueber primäres Lungencarcinom. Dissert., Jena, 1901.

11 Davis and Le Count. Chicago Path. Soc., 1908, VII No. 5.

8 DAVIS AND LE COUNT<sup>11</sup> 1908 F, 32 Dyspnea, cough, blood-stained sputum, hoarseness, left chest fixed and bulging, mucosa of chief bronchi resembled skin, left main bronchus almost occluded by squamous celled carcinoma, left lung aimless, metastases in tracheal and retro aortic nodes, pleura, liver, both adrenals, both kidneys and both ovaries

9 DOMENY<sup>12</sup> 1902 M Sharp pain in left side, cough with scanty sputum, medullary carcinoma of bronchus to left lower lobe, atelectasis of that lobe, emphysema of right lung, secondaries in lymph-nodes and right kidney, origin from bronchial epithelium

10 DÓMENY<sup>12</sup> 1902 F, 79 Right hydrothorax, carcinoma of left main bronchus, branch to lower lobe nearly obstructed, large nests of polygonal cells, secondaries in bronchial nodes

11 DOMENY<sup>12</sup> 1902 M, 41 Pain in head, auditory and visual disturbances, choked disk on both sides, cylindric celled adenocarcinoma of bronchus to left lower lobe, that lobe atelectatic, seven brain metastases, origin from mucous glands

12 DOMENY<sup>12</sup> 1902 F, 66 Fever, cough, pain in right side, dyspnea, dullness below angle of scapula on the right, cylindric celled adenocarcinoma of bronchus to upper right lobe, secondaries in bronchial and mediastinal nodes, origin from mucous glands

13 DÓMENY<sup>12</sup> 1902 M, 29 Pain in left arm, tumor masses on ribs, sternum and cranium, adenocarcinoma of bronchus to left lower lobe, secondaries of cranium, ribs, sternum, liver, retrobronchial and retroperitoneal nodes, brain, right kidney, much mucus formation, especially in metastases, origin from mucous glands

14 DORSCH<sup>13</sup> 1886 (After Passler) F, 54 Two medullary masses in right upper lobe, growing from right chief bronchus and involving pericardium and vena cava, the latter thrombosed, large polymorphous cells, metastases in lymph-nodes at hilus, lung tissue of same side, liver, spleen, kidneys, sternum, dura mater

15 EHRLICH<sup>14</sup> (After Adler) 1891 M, 51 Dulness over upper right, hemoptysis, cancerous tissue in sputum, large node in right axilla, alveolar carcinoma of right main bronchus, polymorphous cells, secondaries in pericardium, chest wall, bronchial nodes and diaphragm, origin from mucous glands

16 EHRLICH<sup>14</sup> (After Adler) 1891 F, 56 Clinical diagnosis, tumor of mediastinum, alveolar carcinoma of lower trachea, right chief bronchus and its branches, polymorphous cells, right lung atelectatic, metastases in bronchial and mediastinal lymph-nodes, left lung, liver, heart

17 ERNST<sup>15</sup> 1896 M, 50 Cerebral symptoms, cough and mucopurulent sputum, bronchus to right upper lobe occluded by papilliferous growth, squamous celled carcinoma, metastases in left adrenal, cerebrum and cerebellum

18 FRANKEL<sup>16</sup> 1904 M, 52 Laborer Pain in left chest, cough, blood-stained sputum, enlarged inguinal gland found to be carcinomatous, occlusion of left main bronchus by cylindric celled carcinoma, secondaries in inguinal and tracheal nodes

19 FRANKEL<sup>16</sup> M, 40 Chill, high fever, dyspnea, mucopurulent sputum, later dirty brown, bronchus to right lower lobe nearly occluded by a cylindric celled carcinoma, bronchiectasis, secondary involvement of nodes at hilus

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12 Domeny Ztschr f Heilk, Wien, 1902, VIII, 407

13 Dorsch Ein Fall von primären Lungenkrebs, Inaug Dissert, Tübingen, 1886

14 Ehrlich Ueber das primäre Bronchial und Lungencarcinom Dissert, Marburg 1891

15 Ernst, P Beitr z path Anat, etc, Jena, 1896, VI, 155

16 Frankel, A Spezielle Pathologie u Therapie der Lungenkrankheiten, 1904

20 FRIEDLANDER<sup>17</sup> (after Pisslei) 1885 M White medullary mass proceeding from left upper lobe bronchus, no metastases, squamous celled carcinoma with epithelial pearls

21 GARBAT<sup>18</sup> 1909 M, 64 Insurance agent Asthenia, emaciation, cough, blood stained sputum, night sweats, tumor mass over right scapula found to be carcinoma, central portion of right lung involved in mass of carcinomatous growth with mucus containing alveoli, origin from mucous glands, secondaries in liver, both lungs bronchial supraclavicular and retroperitoneal nodes, old tuberculosis of left apex



Fig 2—Section from the bronchial adenocarcinoma shown in Fig 1 The alveolar spaces are filled with mucin Zeiss obj "B"

22 GEORGI<sup>19</sup> 1879 M, 60 Blacksmith History of trauma, cough developed with scanty sputum becoming bloody, died one year later, medullary carcinoma at hilus of left lung, bronchiectasis, upper left lung atelectatic, right emphysematous, no metastases

23 GEIPEL<sup>20</sup> 1899 M, 70 Cigar maker Symptoms of some severe pulmonary disease upper main branch of left chief bronchus almost occluded by an alveolar cylindrical celled carcinoma, secondaries in left lower lobe, origin from bronchial mucosa

17 Friedlander Fortsch r d med, 1885, 1, 307

18 Garbat, A L Am Jour Med Sc, 1909, N S, cxxxvii, 857

19 Georgi Berl klin Wchnschr, 1879, xxviii and xxx

20 Geipel Centralbl f Allg Path u path Anat, 1899, 1, 848

24 GOUGEROT<sup>21</sup> 1905 M, 46 Old tuberculosis, dyspnea, cough, mucopurulent sputum with Koch bacilli, dulness in upper right, polyuria, right main bronchus obstructed by growth which extended throughout upper portion of lung, squamous celled carcinoma with pearls, metastases in peribronchial nodes and left kidney

25 HALL AND TRIBE<sup>22</sup> 1905 M, 17 Cough, dyspnea, cachexia, blood-tinged sputum, glycosuria, columnar celled carcinoma of bronchus to left lower lobe, secondaries in upper left lobe, liver, retroperitoneal and cervical nodes and calvarium

26 HAMPELN<sup>23</sup> 1897 M, 57 Chronic bronchial catarrh, emphysema, asthenia, bloody expectoration, dyspnea, primary bronchial carcinoma with polymorphous cells, origin from mucous glands, no metastases

27 HANDFORD<sup>24</sup> 1888 M, 64 Collier Cough, dyspnea, rapid wasting, history of trauma received five months previously, blood-stained sputum, dulness over upper left thorax, growth beginning three quarters of an inch above tracheal bifurcation and extending along left chief bronchus, nearly filling lumen, secondaries in left lung, pleura and liver, origin from bronchial mucosa, right lung emphysematous

28 HANDFORD<sup>25</sup> 1889 M, 63 Pain after taking food, cough, vomiting, weakness, no dulness, medullary carcinoma completely occluding lower primary division of left bronchus, left lower lobe collapsed, secondaries in liver and bronchial nodes, stomach symptoms due to ulcer

29 HENRICI<sup>26</sup> 1912 M, 62 Cough, bloody sputum, flatness on right between clavicle and fourth rib, squamous celled carcinoma of bronchus to right upper lobe, origin from bronchial mucosa

30 HINTERSTOISSEN<sup>27</sup> 1889 M, 59 Lieutenant colonel History of trauma, glandular swelling of left side of neck and right axilla, pain in left arm, tumor of right ring finger was found to be carcinoma, paralysis of left vocal cord, sputum often bloody and diagnosis made from cells in sputum, carcinoma simplex involving bifurcation and both main bronchi, secondaries in right axillary, left supraclavicular, bronchial and mediastinal nodes and terminal phalanx of right ring finger

31 HITZ<sup>28</sup> (after Adler) 1887 F, 40 Fever, cough, dyspnea, dysphagia, bloody sputum, alveolar carcinoma of right main bronchus, bronchiectasis of right lung, emphysema of left, secondaries in regional lymph-nodes

32 HORN<sup>29</sup> 1907 F, 18 Cough, dyspnea, pain in left thorax, hemoptysis, sudden death, left lung atelectatic, bronchiectasis, left main bronchus completely occluded by carcinoma of glandular structure, spaces contained colloid-like material, origin from bronchial mucosa

33 JAPHA<sup>30</sup> (after Adler) 1892 M, 48 Dyspnea, pain, cyanosis, pleural effusion, dilated veins over thorax, bloody sputum with cancerous particles, cylindric and squamous celled carcinoma developing from hilus along right bronchial tree, metastases in lymph-nodes, pleura and pericardium, origin from bronchial mucosa

34 KARRNSTEIN<sup>31</sup> (after Adler) 1908 M, 48 Hemoptysis, pain in right chest, dulness over right lung, bronchoscope showed tumor in right bronchus,

21 Gougerot, H Bull et mém Soc anat de Par, 1905, lxx, 294

22 Hall and Tribe Lancet, London, 1905, i

23 Hampeln, P Ztsch f klin Med, Berlin, 1897, xlvii, 247

24 Handford, H Tr London Path Soc, 1888-9, xl, 40

25 Handford, H Tr London Path Soc, 1889-90, xli, 37

26 Henrici Jour Med Research, 1912, xxvi, 395

27 Hinterstoiszen, H Wien klin Wchnschr, 1889, ii, 374

28 Hitz Ein Beitr z Casuistik des primären Lungencarcinoms Dissert, Zürich, 1887

29 Horn, O Virchows Arch f path Anat, 1907, cxlxxix, 414

30 Japha Ulcer primären Lungenkrebs Dissert, Berlin, 1892

31 Karrenstein Charité Ann, 1908, xxxii, 315

squamous celled carcinoma with pearls, metastases in liver, stomach, kidneys, brain (?) and pericardium, origin from bronchial mucosa

35 KIDD<sup>32</sup> 1892 M, 52 Butcher Cough for twelve months, pain in left side, blood streaked sputum, dyspnea, dulness and feeble breath sounds on left, tumor at bifurcation and along left chief bronchus and branch to upper lobe, bronchiectasis, atelectasis on left, secondaries in adrenal and jejunum (?)

36 KUBER<sup>33</sup> (after Adler) 1898 F, 34 Apparently healthy, sudden death following burn, glandular carcinoma with small cuboidal cells completely obstructing right lower main bronchus, bronchiectasis in right lower lobe, no metastases, origin from mucous glands

37 KOERNER<sup>34</sup> 1888 M, 64 Money lender Cough, bloody sputum, flatness and absent fremitus on right, severe dyspnea, right lung emphysematous, carcinoma occluding right chief bronchus

38 KRITSCHMER<sup>35</sup> (after Adler) 1904 M, 51 Clinical diagnosis purulent bronchitis, bronchiectasis, pleurisy, diabetes, alveolar carcinoma of left lower bronchus, no metastases origin from mucous glands

39 KRITSCHMER<sup>35</sup> (after Adler) 1904 M, 68 Left sided pleural effusion, adenomatous carcinoma of left main bronchus, metastases in bronchial, mediastinal, retroperitoneal nodes, left kidney, liver, both adrenals Origin from mucous glands

40 KUBER<sup>36</sup> 1906 M, 36 Pain in chest, cough, dyspnea, loss of weight and strength Cylindric celled carcinoma arising from mucosa of trachea and bronchi, proliferating along bronchial ramifications and obstructing lumina, diagnosed from metastases

41 LANGHANS<sup>37</sup> 1871 M, 40 Symptoms of right bronchial stenosis, died suddenly in a "suffocative attack", alveolar carcinoma at tracheal bifurcation and along wall of right bronchus, small polyhedral cells, no secondaries, origin from mucous glands

42 LARDILLON<sup>38</sup> (after Adler) 1903 M, 60 Cough, emaciation, asthenia, mucopurulent sputum, alveolar carcinoma of left main bronchus, polymorphous cells bronchiectasis and atelectasis of left lung, secondaries in nodes at left hilus

43 LETULLE AND BIENVENUE<sup>39</sup> (after Adler) 1908 F, 63 Emaciation, hoarseness, dyspnea, blood stained sputum, alveolar carcinoma of left main bronchus, polymorphous cells, secondaries in tracheal and bronchial nodes and adrenals origin from bronchial mucosa

44 MAUN<sup>40</sup> (after Adler) 1905 M, 50 Asthenia, abundant hemoptysis, alveolar carcinoma of left main bronchus, secondaries in bronchial nodes, pericardium, left ventricle origin from bronchial mucosa

45 MCINTYRE<sup>41</sup> 1912 N, 67 Dyspnea, cough, bloody sputum, dulness over upper left, adenocarcinoma of bronchus to upper left lobe, no metastases, tuberculosis also present

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32 Kidd, P Tr Clin Soc London, 1892, xlv, 178

33 Kluber Ein Fall von Bronchialcarcinom und Lungencyste Dissert, Erlangen, 1898

34 Koerner, O Munchen med Wehnsch, 1888, xxxv, 178

35 Kretschmer Ueber das primäre Bronchial- und Lungenkarzinom Dissert, Leipzig, 1904

36 Kuber Centralbl f inn Med, 1906, No 44, p 1089

37 Langhans Virchows Arch f path Anat, xlii, 470

38 Lardillon Contribution à l'étude du cancer des poumons Thèse de Lyon, 1903

39 Letulle et Bienvenue Bull et mém Soc méd d hôp de Paris, 1908, xxv, Series 3, p 610

40 Maun, J Deutsch med Ztschr, 1905, xxi, 537

41 McIntyre Glasgow Med Jour, 1912, lxxviii, 95

46 MERKLEN AND GIRARD<sup>42</sup> (after Adler) 1901 M, 45 Dyspnea, dysphagia, aphonia, dullness over right lung, blood-streaked sputum, alveolar carcinoma of right main bronchus, no metastases

47 MEUNIER<sup>43</sup> 1895 M, 70 Cabinet maker Extreme dyspnea for eight days, semi-stuporous, cough, sputum blood-tinged, healed tubercles in left apex, tumor mass at hilus of right lung, alveolar structure, polyhedral cells, origin from bronchial glands

48 MINNSEN<sup>44</sup> (after Adler) 1900 M, 43 Pain in right chest, cough, dyspnea, bloody sputum, alveolar carcinoma of right lower lobe bronchus, some mucus formation in neoplasm, secondaries in left pleura, bronchial and retroperitoneal nodes, pancreas, spleen, kidneys, origin from mucous glands

49 OGLE<sup>45</sup> 1893 F, 48 Left bronchus completely obstructed by polypoid growth near bifurcation, purulent material in bronchi, alveolar carcinoma, metastases in bronchial nodes

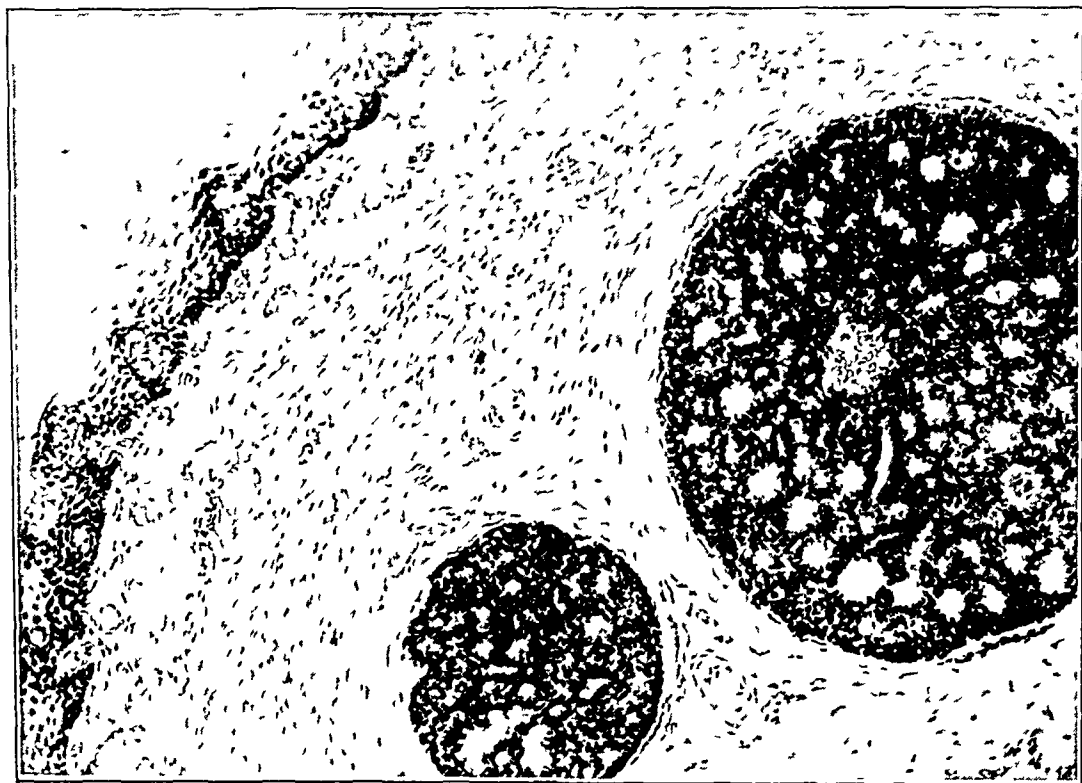


Fig 3—Wall of esophagus showing ingrowth of bronchial adenocarcinoma by direct extension Zeiss obj "B"

50 PACKARD<sup>46</sup> 1905 M, 55 Cigarmaker Cough, dyspnea, bloody sputum, dilated veins over thorax and flatness over entire right, with absent fremitus, enlarged abdomen, lymph-nodes in both axillae Death from hemorrhage Squamous celled carcinoma involving all of right main bronchus and part of left, secondaries in left lung and pleural surface of diaphragm

51 PASSLER<sup>5</sup> 1896 M, 73 Pensioned policeman Cough and sputum, never bloody, left recurrent laryngeal paralysis, medullary cylindric celled carcinoma

42 Merkel and Girard Bull et mém Soc méd d hôp de Paris, 1901, xviii, Series 3, p 760

43 Meunier, H Arch gén de méd, Par, 1895, 1, 343

44 Minssen Ueber primären Lungenkrebs Dissert, Kiel, 1900

45 Ogle, C Tr London Path Soc, 1893-4, xlv, 25

46 Packard, M Med News, New York, 1905, lxxvi, 303



of left chief bronchus compressing trachea, bronchiectasis in left lung, emphysema in right, secondaries in both kidneys

52 PASSIR<sup>5</sup> 1896 M, 52 Chronic laryngitis, repeated hemorrhages, small ulcerating squamous celled carcinoma of right main bronchus, fatal hemorrhage from erosion of right pulmonary artery

53 PASSIR<sup>6</sup> 1896 M, 63 Nearly complete right sided hemiplegia, cachexia Carcinoma of bronchus in left lower lobe, metastases in right lower lobe, liver, cerebrum and cerebellum, cylindric cell type with some mucous degeneration

54 PAROW<sup>7</sup> (after Adler) 1896 M, 62 Dyspnea, cachexia dysphagia Tumor in right supraclavicular region cylindric and polymorphous celled carcinoma of right main bronchus and first portion of left, metastases in cervical and supraclavicular nodes Origin from bronchial mucosa

55 PEABODY<sup>8</sup> 1891 M, 33 Stevedore Cough, mucoid expectoration, pain in left chest impaired resonance over left hyperresonance over right side, tumor mass  $2\frac{1}{4}$  inches in diameter in and around left chief bronchus, metastases in lungs

56 PERITZ<sup>9</sup> (after Adler) 1896 M, 48 Pain in right chest, cough, dyspnea, cachexia, flatness over entire right bloody sputum, enlarged axillary and cervical nodes, alveolar cylindric celled carcinoma of right main bronchus, secondaries in mediastinal mesenteric, axillary and cervical nodes, and liver Origin from ducts of mucous glands

57 PITT<sup>10</sup> 1887 F, 67 Dyspnea, lessened motility of right chest right main bronchus almost occluded by surrounding growth bronchiectasis of right lung Carcinoma of a glandular scirrhous type metastases in left lung and right supraclavicular nodes

58 RLINHARD<sup>1</sup> 1878 M, 47 Wainisher Hoarseness, dyspnea, evanosis swelling of face and neck pain in chest Alveolar carcinoma of bronchus to right upper lobe, compressing superior vena cava, left lung emphysematous Origin from mucous glands (?)

59 ROSENTHAL<sup>11</sup> (after Adler) 1899 F, 52 Hemiplegia and other cerebral symptoms, some cough and dyspnea Alveolar cylindric celled carcinoma of left main bronchus, secondaries in brain bronchial and tracheal nodes and left ventricle

60 SCHROETTLER<sup>2</sup> (after Nage) 1907 F, 57 Paralysis of left recurrent laryngeal Squamous celled carcinoma at bifurcation of trachea completely blocking left chief bronchus

61 SEHRT<sup>3</sup> (after Adler) 1904 M, 66 Alveolar squamous celled carcinoma of right main bronchus Secondaries in bronchial and tracheal nodes, bronchiectasis, chronic tuberculosis, fatal hemorrhage following erosion of pulmonary artery

62 SEHRT<sup>3</sup> (after Adler) 1904 M, 68 Dyspnea, dulness over left chest, hemoptysis Squamous celled carcinoma of left main bronchus, secondaries in bronchial lymph nodes and esophagus, chronic tuberculosis

47 Parow Ein Fall von primären Lungencarcinom Dissert, Greifswald, 1896

48 Peabody, G. L. Med. Rec., New York, 1891, *xxxx*, 438

49 Peritz Ueber Brusthöhlen Geschwulste Dissert, Berlin, 1896

50 Pitt, G. N. Tr. London Path. Soc., 1887-8, *xxxx*, 54

51 Rosenthal Ueber einen Fall von primären Lungencarcinom Dissert München, 1899

52 Schrotter Klinik der Bronchoskopie, 1907 Quoted by F. R. Nage in Arch. f. Laryngol. u. Rhinol., Berlin, 1907, *xx*, 275

53 Sehart Beiträge zur Kenntniss des primären Lungencarcinoms Dissert Leipzig, 1904

63 STIEB<sup>54</sup> (after Adler) 1900 M, 50 Patient died of cirrhosis of liver Submucous squamous-celled carcinoma of bronchus to left lower lobe, secondaries in regional lymph nodes

64 STIEB<sup>54</sup> (after Adler) 1900 M, 60 Cough, pain, weakness Alveolar squamous-celled carcinoma at bifurcation of right main bronchus, secondaries in both lungs and supraclavicular nodes

65 STILLING<sup>55</sup> 1881 M, 52 Alveolar carcinoma of bronchus to right middle lobe, large polygonal cells, metastases in bronchial, mediastinal and cervical nodes, pericardium and liver

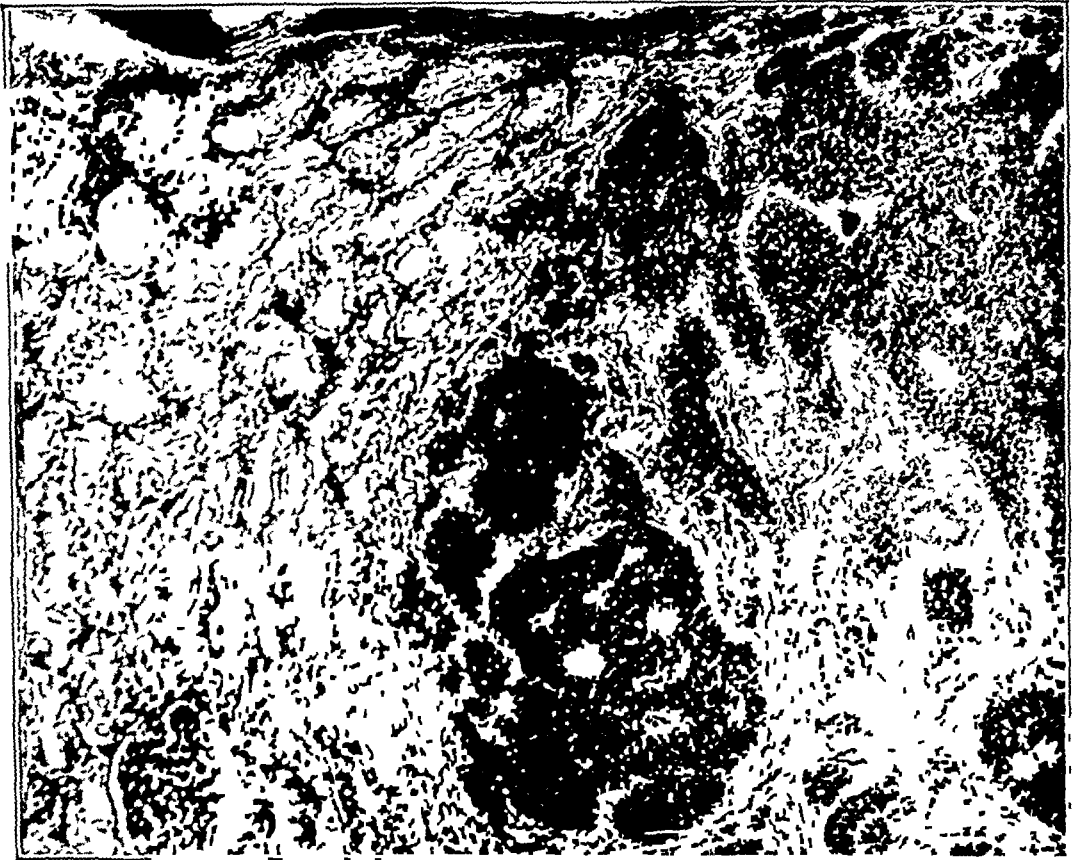


Fig 4—Metastatic growth in kidney from primary bronchial adenocarcinoma The mucus formation is still present but not as marked as in the primary growth Zeiss obj "B"

66 STROPENI<sup>56</sup> 1910 F, 35 Housekeeper Pain in side, back and shoulder, cough, sputum blood-streaked Subcutaneous carcinomatous nodule of left arm, fracture of left femur, left lung atelectatic, right lung emphysematous Adenocarcinoma from mucous glands of left chief bronchus, secondaries in both lungs, epicardium liver, both kidneys, spleen, right femur, thoracic and lumbar vertebrae and cranial vault

67 TURNBULL AND WORTHINGTON<sup>57</sup> (after Adler) 1908 M, 56 Symptoms mainly referable to cord lesion Mucus secreting carcinoma of bronchus to right lower lobe secondaries in seventh and eighth dorsal vertebrae and in ribs

54 Stieb Ueber das Plattenepithelcarcinom der Bronchien Dissert Giessen, 1900

55 Stilling Virchows Arch f path Anat 1881 LXXXVII 77

56 Stropeni L Ztschr f Krebsforsch Berlin 1910 IX 1-21

57 Turnbull and Worthington Arch Path Inst London Hosp, 1908, II, 163

68 SCHRÖTTER<sup>58</sup> 1907 M, 44 Cough and stabbing pain in right side, dilated veins on left chest, abdomen and arm, bloody sputum Specimen from right main bronchus was found to be squamous celled carcinoma with glycogen containing cells, tuberculosis in right apex, emphysema of left lung

69 WAGNER<sup>59</sup> 1903 Cylindric celled carcinoma of left chief bronchus Lumen of bronchus obstructed by cauliflower growth, metastases in left lung, anterior mediastinum, left lobe of liver Origin from bronchial mucosa

70 WATSUJI<sup>60</sup> M, 56 Mucosa reddened and broken at origin of left chief bronchus Near hilus a large tumor mass completely infiltrating bronchial wall, right lung emphysematous, squamous celled carcinoma Origin from bronchial mucosa

71 WATSUJI<sup>60</sup> 1904 M, 60 No clinical history Squamous celled carcinoma of left chief bronchus, metastasis in a bronchial node which also contained a caseating tubercle

72 WATSUJI<sup>60</sup> 1904 M, 59 Squamous celled carcinoma of right lower lobe bronchus, right lung atelectatic, patient was also tuberculous

73 WATSUJI<sup>60</sup> 1904 Microscopical report without history or protocol, sections showed change of epithelium of a lower lobe bronchus into squamous type, wide peripheral extension from this bronchus

74 WATSUJI<sup>60</sup> 1904 M, 64 Tumor mass at point of division of bronchus to middle lobe, squamous cell type with hyaline pearls

75 WEINBERGER<sup>61</sup> 1901 M, 42 Beadle History of bronchitis and influenza, fever, cough, bloody sputum, stridor, dulness over upper right Cylindric celled carcinoma of secondary bronchus in right upper lobe, metastases in right infra and supraclavicular and axillary nodes

76 WEINBERGER<sup>61</sup> 1901 M, 52 Clerk Pain in right chest, cough dyspnea Blood-tinged sputum with carcinomatous tissue, walnut sized tumor of parietal bone, right main bronchus completely obstructed by carcinoma, metastases in liver, kidney, muscles, intestines, parietal bone and brain

77 WERNER<sup>62</sup> 1891 M, 65 Farm laborer Bloody sputum for ten weeks, pain in right axilla, hip, left forearm, atypical epithelial cells in sputum, three lower spinous processes painful, tumor of bronchus to upper left lobe, glandular structure, metastases in left arm (fracture), lower vertebrae, neck of right femur

78 WEST<sup>63</sup> 1884 M, 39 Laborer Dyspnea, emaciation, asthenia, night sweats, dulness over lower right Carcinoma surrounding right main bronchus, reducing its lumen to one third, secondaries in bronchial nodes and liver

79 WOLF<sup>64</sup> 1895 M, 60 Symptoms of cavitation Cylindric celled carcinoma encircling and stenosing left chief bronchus 2 cm below the bifurcation, bronchiectasis, metastases in liver and bronchial nodes

80 WOLF<sup>64</sup> 1895 M, 54 Musician Anorexia, asthenia, emaciation, in left chief bronchus an ulcerating tumor obliterating its branches, left lung small and firm, right lung emphysematous Cylindric celled carcinoma, metastases in bronchial glands and peritoneum

81 WOLF<sup>64</sup> 1895 M, 47 Blacksmith Pain in right side, dry cough, dyspnea, dulness and bronchial breathing on right right chief bronchus entirely closed by tumor reaching 15 cm above the tracheal bifurcation, bronchiectasis on right, left lung emphysematous Carcinoma simplex, large polymorphous cells, secondaries in lungs, dura mater and liver

82 WOLF<sup>64</sup> 1895 M, 42 Factory hand Clinical picture was that of brain tumor, right chief bronchus partially closed and its mucosa ulcerated, tumor

58 v Schrutter Ztsch f klin Med, 1907, 111, 508

59 Wagner Munchen med Wehnsch, 1903, 1, 133

60 Watsuji, S Ztschr f Krebsforsch Jena, 1903 4, 1 445

61 Weinberger Ztschr f Heilk, 1901, 11, 78

62 Werner, M Das primäre Lungencarcinom etc, Dissert, Freiburg 1891

63 West Tr London Path Soc, 1884, 111, 87

extends into both upper and lower lobes Alveolar carcinoma with large polymorphous cells, metastases in spleen, kidneys and brain

83 WOLF<sup>3</sup> 1895 M, 58 Epistaxis, dyspnea, dulness over right apex, sputum became bloody, right main bronchus filled with cauliflower growth, left lung very emphysematous Glandular celled carcinoma, secondaries in lungs, dura mater, nasal septum

84 WOLF<sup>3</sup> 1895 M, 55 Mechanic Bilateral hydrothorax, wall of right main bronchus thickened, bronchiectasis on right Carcinoma, alveolar in structure, large oval cells, metastases in liver, portal vein, retroperitoneal nodes and seventh and tenth thoracic vertebrae

85 WOLF<sup>3</sup> 1895 M, 56 Servant Dyspnea, weakness, hemoptysis, dulness with bronchial breathing over entire left left chief bronchus completely filled with tumor invading lower 3 cm of trachea and constricting right bronchus, emphysema of right lung Carcinoma, alveolar in structure, secondaries in thyroid and both adrenals Origin from bronchial glands

86 WOLF<sup>3</sup> 1895 M, 67 Collector Dyspnea, dysphagia, pain in left arm, flatness on percussion over upper left, death from suffocation, left chief bronchus occluded by growth from its own wall Squamous-celled carcinoma, metastases in pericardium and retroperitoneal lymph-nodes

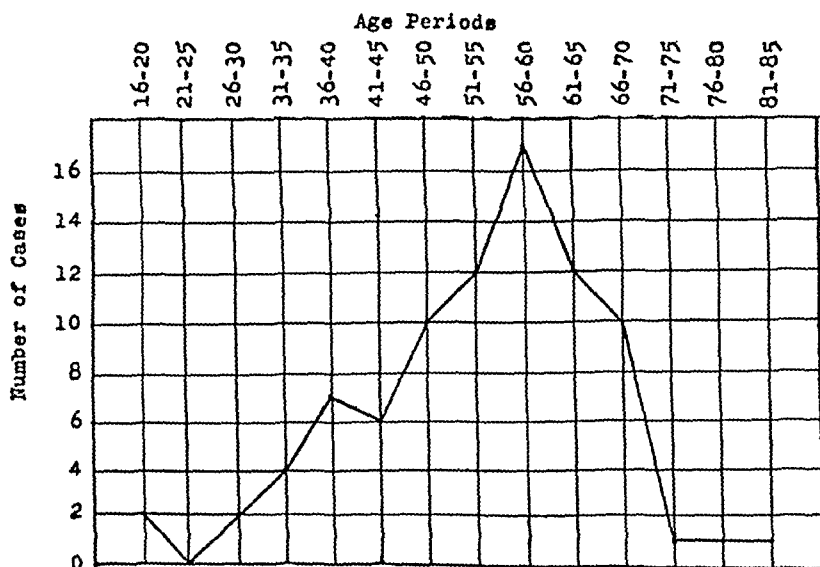


Fig 5—The age incidence of primary bronchial carcinomata by five year periods, based on a total of eighty-five cases The abscissae indicate the number of cases, the ordinates the age periods

87 WOLF<sup>3</sup> 1895 M, 69 Mechanic Clinical picture was that of phthisis, in right chief bronchus, 3 cm below bifurcation, an oval ulcerated area, bronchiectasis on right Squamous celled carcinoma, metastases in bronchial lymph-nodes and liver

88 WOLF<sup>3</sup> 1895 M, 54 House porter Abscess over eighth rib Squamous-celled carcinoma blocking right main bronchus from bifurcation down, perforating superior vena cava and compressing right innominate, tuberculosis in pleura and right apex, secondaries in both kidneys and left adrenal

89 WOLF<sup>3</sup> 1895 M, 65 Mechanic Clinical picture dominated by cerebral symptoms, tumor mass beneath eroded area in right chief bronchus, bronchiectasis Squamous celled carcinoma, metastases in right cerebral cortex and bronchial nodes

The following case from the Medical Service of the University hospital also belongs in this group

*History*—Male aged 47 (?), awning-maker Brought to the hospital in an unconscious condition at 9 30 a m, November 12, 1911 Only a brief history

could be obtained from the patient's friends. He had not been as well as formerly for two years. Marked dyspnea for some time, with epistaxis and hemoptysis. The patient had believed that he had asthma, and stramonium leaves were found in his pockets. He became unconscious while seated in a chair in a hotel lobby.

*Examination*—The following notes are taken from the hospital records. The patient was intensely cyanotic, skin dry, pupils evenly and markedly contracted, reacting but very little to light. There was marked dyspnea, with great activity of the accessory muscles. Respiration characterized by a short deep inspiration and long expiratory period. The rate was but 10 or 12 per minute. There were many rales during inspiration. No area of dullness was detected.

The heart was regular, apparently not enlarged, and the heart sounds were of good quality, the rate, 110. The radial pulse was of good size, quick, and fairly compressible.

The patient moved both arms readily but no spontaneous movements of the legs were noted.

The urine obtained by catheterization, was negative except for a heavy trace of albumen. Tests for morphin applied to the urine were negative. Stomach washings contained only a little slimy mucus and a few fine particles of food.

The rectal temperature was 97.8 and 96.1°.

*Treatment*—A coffee and whiskey enema was retained. The stomach was washed with potassium permanganate solution 1 to 500 and 1/150 gr. doses of atropin administered on the assumption that the case might be one of morphin poisoning. Oxygen was also used, and strychnin in 1/30 gr. doses.

Death occurred at 1.35 p. m. of the same day. Respiration ceased about one minute before the heart stopped beating.

*Necropsy*—The autopsy was performed by Dr. A. S. Warrin at 9.00 a. m., Nov. 13, 1911. The more important points in the protocol dictated by Dr. Warrin are included below.

Thorax long, epigastric angle less than a right angle, superficial veins not dilated, a small amount of blood stained mucus in the mouth.

Skull cap very thin, otherwise negative, dura adherent all over the convexity, arachnoid slightly thickened, convolutions pale and edematous, section of brain otherwise negative.

No free fluid or gas in peritoneal cavity. Liver in median line two finger breadths below the ensiform. The diaphragm rises to the level of the fifth rib on the right and the sixth rib on the left.

No free gas or fluid in the thoracic cavity. There are a few small adhesions between the visceral and parietal pleurae, most marked at the right apex where the pleura shows a dense hyaline thickening, no enlarged lymph nodes in the anterior mediastinum.

Apex of the heart at the sixth interspace in nipple line. Auricles, particularly the right distended with unclotted blood. Mitral orifice somewhat larger than normal, admitting two fingers with ease, tricuspid admits four fingers, valve flaps negative.

Orifices and valve flaps of pulmonary artery and aorta negative. No narrowing of lumen of aorta and no aneurysm.

Left lung. Anterior border extends to left sternal line. Large bronchi filled with creamy exudate, bronchial nodes small and heavily pigmented, moderately voluminous, marked congestion and edema.

Right lung. Anterior border extends to right sternal line. The lung is bound by many adhesions to a tumor the size of an orange which is connected with the bronchial nodes, the esophagus and the descending aorta. The tumor mass completely surrounds the main bronchus to the right lung and has infiltrated and destroyed the bronchial wall. The lumen of the bronchus is markedly narrowed (Fig. 1). The tumor also extends along the bronchus to the upper lobe.

At the level of the bifurcation the trachea is much stenosed by the pressure of the tumor mass. This stenosis affects the left main bronchus more than the right. The former barely admits a glass rod 2 mm. in diameter. The lumen of

the esophagus is also narrowed at the same level and the wall is firmly attached to the tumor mass

**Spleen** Small, capsule slightly wrinkled and contains numerous small hyaline thickenings, atrophy of pulp and follicles, increase of stroma

**Left kidney** Fibrous capsule strips easily On section the parenchyma is deep purplish red, bleeds freely Several small grayish nodules beneath the surface

**Right Kidney** Shows less passive congestion than the left, otherwise similar

**Adrenals** Normal in size medulla preserved

**Large and Small Intestines** Partially distended with gas duodenum negative, pylorus patent, stomach mucosa slightly atrophic, no erosions or hemorrhages

**Pancreas** Congested and softer than normal

**Liver** Capsule somewhat thickened and contains small hyaline areas, parenchyma shows a marked acute passive congestion, gall bladder shows old adhesions

**Abdominal aorta** shows patches of sclerosis and atheroma

**Retroperitoneal lymph nodes** are atrophic and congested

*Microscopical Findings*—The most important microscopical findings follow

**Heart** Atrophy, fatty degeneration, arteriosclerosis of coronaries

**Spleen** Atrophy, chronic passive congestion, acute congestion, hyaline thickening of capsule

**Brain** Congestion, edema, chronic leptomeningitis

**Kidneys** Acute passive congestion, atrophy, cloudy swelling, metastatic adenocarcinoma

**Right Lung** Chronic abscess, chronic fibroid pneumonia, bronchiectasis, chronic passive congestion

**Left Lung** Emphysema, chronic passive congestion

**Liver** Atrophy, chronic passive congestion, hyaline areas in capsule are thickenings with hyaline blood-vessels, probably nearly healed angiocavernosa

**Pancreas** Atrophy, sclerosis, post mortem change

**Neoplasm** After formaldehyd fixation and paraffin infiltration, sections of the neoplastic tissues were stained in hematoxylin and eosin, carbol kresyl-echt-violett, Bismarck brown and hematoxylin and picric acid The primary tumor mass shows an adenocarcinoma with irregular gland-like spaces (Fig 2) which are lined by two or more rows of epithelial cells, with large spherical or oval nuclei There is some tendency for the oval nuclei to be arranged with their long axes parallel to each other and perpendicular to the lumina, giving a marked cylindric celled appearance The cell nuclei stain readily but not intensely with the various basic stains The alveolar spaces are filled with a finely granular material which takes a bluish stain with hematoxylin and reacts metachromatically with carbol kresyl-echt violet, thus resembling mucin in every particular

The same architectural and cell characteristics are found in all parts of the neoplasm examined In the more peripheral portions of the growth such as the part invading the esophageal wall (Fig 3) the alveolar spaces are smaller Even in the metastases in the kidney (Fig 4) mucin formation has taken place

The neoplasm must be considered a primary adenocarcinoma of the right main bronchus, cylindric celled in character, probably arising from the bronchial mucous glands

#### GENERAL CONSIDERATIONS

*Frequency*—The number of cases reported indicates that bronchial carcinoma is not as rare a disease as has been supposed Wolf<sup>3</sup> found lung and bronchial carcinomata in 223 per cent of 20,116 autopsies and Passler considers 87 per cent of the neoplasms in this group to be of bronchial origin The difficulty in diagnosing the condition has done much to keep down the percentage but now that its frequency of occur-

ience is more fully realized and search is being made for it, the ratio of incidence is being raised. This is shown by the statistics of the combined lung and bronchial group which Adler<sup>1</sup> presents in his monograph. A summation of the more recent statistics gives forty cases in a total of 11,093 autopsies, that is, 36 per cent.

*Age*—The age was given in eighty-five of the eighty-nine cases in our own list. The distribution over five-year periods is shown by Figure 5. The maximum number is found in the age period 56 to 60, inclusive, but the possibility of occurrence in very young individuals is emphasized by the cases of Hall and Tribe<sup>22</sup> and of Hoin,<sup>29</sup> in which the patients were 17 and 18, respectively.

*Sex*—In eighty-seven cases, seventy patients were males and seventeen females. Passler found the ratio to be fifty males to eighteen females in his list of both lung and bronchial carcinomata. After making due allowance for the usual preponderance of male patients in the hospitals from which many of the cases are derived, it still seems evident that bronchial carcinoma is much more common in males than in females.

*Location*—Much stress has been laid on a supposed excess of cases of carcinoma of the right bronchial tree as compared to the left. Reinhard,<sup>64</sup> for instance, reported eighteen lung carcinomata from the right side and nine from the left. This disproportion has been attributed to the larger size and more direct course of the right main bronchus with the thought that it would be subjected to a greater degree of mechanical irritation than the left. Adler,<sup>1</sup> in his combined lung and bronchial list, finds the right side more frequently affected than the left, but thinks that the difference is too small to serve as a basis for a theory. We find the two sides to be involved with approximately equal frequency.

Left side	28 cases
Right side	27 cases
Both sides	14 cases

*Etiology*—The data in regard to occupation are too meager to permit the drawing of definite conclusions. The case of Boyd,<sup>9</sup> in a bottle-blower, those of Beck,<sup>7</sup> Georigi,<sup>19</sup> and Wolf<sup>3</sup> in blacksmiths, with Handford's<sup>24</sup> in a collier, may be picked from the twenty-five of known occupation as instances in which opportunity for chronic bronchial irritation is obvious. In discussing the etiology of this group, Wolf<sup>3</sup> mentions luetic scars and ulcerations, but puts the most emphasis on a breaking through of softened pigmented lymph-nodes into the bronchial lumen. He says that the "*Pigmentdurchbrüche*" occur especially in the chief bronchi just below the bifurcation and more often on the right side than on the left. This theory has not been supported by the microscopical

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64 Reinhard, W. Arch. d. Heilk., 1878, vii, 369.

findings in subsequent cases, and the part played by dust inhalation requires further study. A very suggestive fact is the preponderance of cases in males who, through occupation and the use of tobacco, are more exposed to the inhalation of irritating substances than are females (Adler<sup>1</sup>).

In but three cases was the disease attributed to trauma. Two of these were from falling (Hinterstoissen<sup>27</sup> and Handford<sup>24</sup>), and the other from a blow on the chest from a piece of iron (Georgi<sup>19</sup>). We may, therefore, be certain that gross trauma is not an important etiological factor.

In a very few instances squamous-celled carcinomata have been described as developing in the walls of bronchiectatic or tuberculous cavities (Kaufmann<sup>67</sup>). The series of cases here reviewed indicates, however, that bronchiectasis is a result rather than a cause of the neoplastic growth. Bronchiectasis is specifically mentioned in fifteen of the case reports, but it occurs in the peripheral portions of the lung rather than at the site of the tumor, and is usually accompanied by atelectasis. It must be considered as due to the stenosis of the bronchus and the inflammatory changes in the lung parenchyma.

In eleven cases out of the eighty-nine a coincident tuberculosis is mentioned. This is usually apical and in two or three instances is spoken of as "old" or "healed." There is nothing to indicate that the tuberculosis was in any way a direct causal factor. It would rather seem that some chronic inflammatory process in the lungs such as tuberculosis, chronic bronchitis or chronic pneumonia, which is also rather frequently found in these histories, may be indirectly the inciting influence. More complete histories of the previous condition of the patient must be had before the importance of these factors can be fully established.

*Point of Origin*—Primary carcinoma of the bronchi may arise either from the bronchial mucosa or from the epithelium of the bronchial mucous glands. Analysis of the cases listed gives the following results.

Origin from mucous glands .	22
Origin from bronchial mucosa	17
Uncertain or unspecified	50

Of the adenocarcinomata, eighteen are referred to a glandular origin and six to the mucosa. All of the squamous-celled type, in which the point of origin is given, are said to have arisen from the mucosa. In the latter case, there is much in favor of the theory that the malignant change is associated with a metaplasia of the surface epithelium to the squamous type. The case of Davis and Le Count is illustrative, for the mucosa was found to resemble skin from a centimeter above the tracheal bifurcation to a point some distance along each of the main bronchi.

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67 Kaufmann *Lehrbuch der Speziellen Pathologischen Anatomie*, p 303



Von Schrotter<sup>58</sup> also argues for a metaplastic origin for the squamous-celled type rather than referring it to an embryonal anlage

In the case here reported the origin was probably from the mucous glands. As in many other neoplasms of similar character, the "*Uebergangsbilder*," which would prove this point, are lacking. However, many sections taken along the main bronchus show small islands of tumor, occupying the normal position of mucous glands, equaling normal mucous glands in size, and themselves containing mucus. At this same point the bronchial mucosa is inflamed and eroded, but nowhere neoplastic. The general architecture of the tumor is also very suggestive of the glandular origin.

*Histopathology*—In fifty-five cases, the general structural character of the neoplasm is given. It is spoken of as

Alveolar, acinar or adenomatous	in 45 cases
Medullary	in 5 cases
Sclerous	in 3 cases
Simplex	in 2 cases

This shows an unduly large number of the first group, for in most of the cases described as "squamous," nothing is said in regard to structure. According to cell type, we find these carcinomata described as

Squamous celled in	25 cases
Cylindric celled in	18 cases
Polymorphous celled in	10 cases
Round or oval celled in	2 cases
Gland celled in	1 case
Cuboidal celled in	1 case

It is probable that most of the cases in the last four groups might have been placed in one or the other of the first two. The two chief forms of bronchial carcinomata are, therefore, the adenomatous cylindric-celled type and the squamous-celled type.

As has been described, mucus formation was a prominent feature in the histological picture of our own case. It is mentioned in ten of those listed, all adenomatous in character. The extent of mucus production varies from the formation of intracellular vacuoles, as in the case of Beck,<sup>7</sup> to the filling of large alveoli with metachromatically staining mucin, as in the cases of Stropen<sup>56</sup> and Domeny.<sup>12</sup> Boecker<sup>8</sup> and Hoin<sup>29</sup> consider that mucus formation does not prove an origin from the bronchial mucous glands, although in most of the other cases such an origin is maintained. Mucus formation in the metastases has been noted in three cases, including our own.

*Metastases*—The proneness of lung and bronchial carcinomata to give rise to metastases has been much emphasized. Wolf<sup>3</sup> found secondaries in twenty-one cases out of twenty-three, Passler,<sup>5</sup> in sixty-three

cases out of seventy-four. The figures from our list of exclusively bronchial carcinomata closely parallel these

Metastases found to be present	70 cases
Metastases not mentioned	11 cases
Metastases not found	9 cases

The locations of the secondary growths were the most varied. Some unusual sites are mentioned, such as in the finger (Hinterstoissen<sup>27</sup>), and nasal septum (Wolf<sup>3</sup>). It is unnecessary to give a complete enumeration of the secondaries found, but the bronchial, cervical and axillary lymph-nodes, liver, kidneys and adrenals were most frequently involved. In the case here reported, the only secondaries were those found in the kidney. Two other observations should be mentioned.

1 The proneness to brain metastases, which are found in twelve cases. The clinical picture may be dominated by such secondaries. Domeny<sup>12</sup> reports a case in which the chief findings were pain in the head, visual and auditory disturbances and choked disk. In this instance there were seven brain metastases from a bronchial adenocarcinoma.

2 The frequent occurrence of palpable secondaries in the lymph-nodes. In thirteen cases such nodes were noted, usually cervical, supra-clavicular or axillary. The reported cases show that, as a rule, if the glands of but one side are invaded the neoplasm will be found to involve the bronchus of the same side.

#### SYMPTOMATOLOGY AND DIAGNOSIS

In a few cases an ante mortem diagnosis of bronchial carcinoma is absolutely impossible. Such cases fall into three groups: (1) those in which the neoplasm is very small and is discovered only incidentally, as in the case reported by Kluber,<sup>33</sup> (2) those in which the clinical picture is dominated by cerebral or other metastases, as in one of Wolf's cases; (3) those in which the patients are practically moribund when first seen. The case here reported falls in the last group.

On the other hand, diagnosis is often possible, as is shown by the fact that in about ten of the cases listed in this paper the nature of the process was ascertained before necropsy. With the additional aids now available the proportion of diagnosed cases should be very much increased.

The chief symptoms mentioned in the clinical histories of the listed cases, in the order of their frequency, are as follows:

1 *Cough*—Sometimes this is spoken of as a "dry" cough, but the case reports give no characteristic description.

2 *Dyspnea*—This very frequent symptom is usually progressive in character, becoming more and more severe, and oftentimes terminating in the death of the patient in a suffocative attack.

3 *Hemoptysis*—Hemorrhage, ranging from a bloody streak in an otherwise mucopurulent sputum to a brisk flow of bright red blood, is one of the most common findings. In forty-two cases in which the character of the sputum is mentioned, there was some degree of hemoptysis in thirty-five. The "black-currant jelly" or "raspberry jelly" sputum once thought to be characteristic of lung and bronchial carcinomata is rarely mentioned in case reports.

4 *Pain*—Pain is also frequently a factor in the clinical picture. It is felt in the chest, usually on the affected side, or in that shoulder and arm. Here it may be explained as a referred pain, or it may be due to pressure on the brachial plexus from a secondary involvement of axillary or clavicular nodes.

5 *Pressure Symptoms*—The group of symptoms arising from pressure of the neoplasm on surrounding structures is of great diagnostic value. From obstruction to the venous return we have dilatation of the superficial veins of head and thorax, often accompanied by edema. These changes are mentioned in nine cases. In five paralysis of the recurrent laryngeal is noted and two others showed aphonia. Dysphagia is reported in four instances, and in one pupillary inequality and ptosis of one lid developed.

The usual absence of fever and night sweats from the symptom complex is worthy of note. In but four of the ninety cases is fever mentioned.

The physical findings vary with the extent of the neoplasm, with the degree of stenosis of the bronchi and with complicating lung conditions. The usual percussion findings are dulness in the lobe or lobes supplied by the affected bronchus and hyperresonance in the opposite lung. The dulness depends largely on atelectasis due to air absorption from the alveoli of the lobes of which the bronchi have been blocked. The hyperresonance is due to a compensatory emphysema in the opposite lung. Signs of cavitation in the affected lung are also frequently found. In the bronchial type of pulmonary carcinoma cavity formation is usually due to bronchiectasis rather than to breaking down of the neoplasm, a process to which it is often erroneously referred. As previously mentioned, bronchiectasis is practically always found in the portion of the bronchial tree beyond the stenosis. In general, it may be said that the physical findings in bronchial carcinoma are those of bronchial obstruction.

*Bronchoscopic examination* may confirm a diagnosis of bronchial carcinoma. Rénon, Géraudel and Marre<sup>65</sup> report such a case (not included in list through lack of autopsy findings), in which the lower portion of the left main bronchus was seen to be entirely obstructed by a neoplastic growth. A piece of the tumor was removed through the bronchoscope, examined microscopically, and found to be squamous-celled in character.

65 Rénon, L. Géraudel et Marre. *Presse méd.*, Paris, 1910, xviii, 401.

*Radioscopy* is of the greatest service in these cases. After describing thirteen cases of lung and bronchial carcinoma which were examined radioscopically, Otten<sup>66</sup> concludes that tumors arising from a large bronchus at the hilus and spreading into the lung as a compact mass, should give little difficulty; that differentiation is difficult when the neoplasm spreads diffusely along the bronchial tree, and that the skiagram gives the most certain information of any method in regard to the precise localization, the manner of spreading and the extent of bronchial neoplasms.

No opportunity should be lost to obtain evidence in regard to the histological character of the neoplasm. This may often be accomplished by the excision of a metastatic growth, as previously mentioned, by removal of a specimen through the bronchoscope, or by careful search of the sputum. The atypical cells were recognized in the sputum in four of the cases in our list. Stropeni<sup>68</sup> said that no symptom was pathognostic except the finding of tumor cells in the sputum, but now bronchoscopic examination and removal of a specimen may be added as an even more satisfactory procedure.

*Treatment*—In the past the diagnosis of bronchial carcinoma has been considered as chiefly of prognostic value. However, in the rapid advance in intrathoracic surgery the condition is becoming an operable one. Ders<sup>68</sup> reports a total resection of a carcinomatous lung, in which case the death of the patient resulted from a septic process developing in the lung stump. In Lenhartz<sup>69</sup> group of cases a resection of a carcinomatous lobe is reported in which the patient remained comparatively well one and a half years after the operation. Kuttner<sup>70</sup> and Sauerbruch<sup>70</sup> have also removed large sections of carcinomatous lungs with success. The early diagnosis of this condition therefore becomes a matter of the greatest importance, for only through an early diagnosis can the patient be offered any hope of relief or cure. With this in view, bronchial carcinoma should always be considered a possibility in diagnosing lung conditions. Patients with cough, dyspnea, hemoptysis or pressure symptoms in various combinations of intensity should be studied by the newer diagnostic methods which have been applied to this condition. In doubtful cases, Adler<sup>1</sup> advises an exploratory thoracotomy.

Modern lung surgery furnishes the greatest incentive for the early diagnosis of bronchial carcinoma, and it is hoped that this study will aid in making such diagnoses possible.

I wish to acknowledge my gratitude to Dr. A. S. Warthin for his supervision and assistance in the preparation of this study.

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66 Otten, M. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, Hamburg, 1906, ix, 369.

68 Ders. *Centralbl. f. Chir.*, 1911, xxxviii, 427.

69 Lenhartz. Cited by Brauer, *Centralbl. f. Chir.*, 1911, xxxviii, 427.

70 Kuttner, Sauerbruch. Cited by Batzdorff. *Centralbl. f. d. Grenzgeb. d. Med. u. Chir.*, 1912, xxi, p. 1.

# THE LOCALIZATION OF IMPULSE INITIATION AND CONDUCTION IN THE HEART \*

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## INTRODUCTION

It has ever and quite naturally been true that the discovery of a new structure immediately has started an effort on the part of investigators to determine the function thereof, and conversely that the discovery of a new function or property has initiated an effort to discover some structure that could be made the seat of such function or property

The history of the localization of impulse initiation and impulse conduction in the heart illustrates in a striking manner these tendencies and their effects. The heart is spontaneously rhythmical. Does it contain a definite structure whose purpose it is to initiate this spontaneous rhythm? Or, again, in the heart, impulses are carried from one part to another. Is this the function of a special structure? Conversely, a structure is found in the heart which conceivably might act as pace-maker, while still another is found which might well serve to carry the excitation waves from point to point in the heart. At once experiments are devised with the object of obtaining answers to these questions. Nothing could be more logical, nor in the long run more certain of gaining the goal than such a course. Nevertheless there is a danger, very well illustrated by the history of these subjects, of accepting the bare inference in either direction as a fact, or of accepting as conclusive experiments which by the investigators themselves are regarded only as suggestive, or, owing to the reasonableness of the inference, there even is a danger that the investigators themselves may be led to draw conclusions from evidence which at the time is obviously insufficient, or which time may show to have been insufficient.

While the main purpose of this paper is to review critically the work that has been done in the effort to localize the functions of impulse initiation and conduction in the heart, it is hoped that it will at the same time serve to illuminate the way to some of the pitfalls and dangers and difficulties that beset investigators in this field of physiology.

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## I THE LOCALIZATION OF IMPULSE INITIATION

## HISTORICAL

The earliest attempt to account for the regularity of the heart's action led the older physiologists into all sorts of futile hypotheses. Down to the year 1813 the term "*organic instinct*" was employed to designate it.<sup>1</sup> Long before this date, however, physiologists were in the possession of facts which might have sufficed for a generalization closely approximating the truth as we now see it. Thus Harvey and some of the older anatomists observed the movements of the venae cavae to continue in some of the lower animals after the auricles had ceased to move. In the search for the *ultimum moriens* of the body, Haller, and perhaps others before him, discovered that in cold-blooded animals the right auricle usually survives death of the organism longer than other parts of the heart. This survival, however, was not attributed to any property of the tissue of the heart, but was thought to be due to the fact that after death the right side of the heart generally contains a greater or less quantity of blood which was supposed, in the time of Haller, to supply the stimulus to the heart.

Much later, in 1811, Nysten was able to confirm Haller from a study of the human species after decapitation by the guillotine. Nysten, indeed, went one step farther, he studied the irritability of various regions of the human heart, using galvanism as the stimulant and found that usually "those parts of the auricle around the entrance of the venae cavae retain their contractility longest."

The sequence of the heart beat in both warm- and cold-blooded animals was also known at this time. But rather than refer this sequence to any definite structure in the heart and possibly under the influence of the iatromechanists, mechanical rather than physiological explanations of the orderliness of the contractions were sought. For instance, according to Haller and Senac, the usual sequence of the several chambers is exactly what one would expect if the blood is the "habitual stimulant on which the movements of the heart depend." In view of the fact that the contraction of the heart occurs in the order in which the blood flows into its different cavities, this conclusion seemed quite satisfactory. The regular sequence of the auricles and ventricles of the empty heart was attributed by Reid,<sup>1</sup> in 1839 to mechanical stimulation of the empty ventricle by the tug of the auricles. Although Reid apparently was not able to free himself entirely of the influence of the prevailing hypotheses, he, nevertheless, records an experiment which led him to suggest in a vague fashion another possible explanation of the sequence of beat. He discovered that an empty heart would beat when all stimuli were removed

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<sup>1</sup> Reid. In Todd's Encyclopedia of Anatomy and Physiology, London, 1839, p. 607.

by placing it in the exhausted receiver of an air pump, and concluded that "we are almost obliged to have recourse to the supposition that there is some innate power in the heart itself"

As an example of another type of mechanical explanation of the transmission of the impulse along the heart may be mentioned here in passing one suggested by Kurschner<sup>2</sup> in 1850. Kurschner ventured to suggest that the valve musculature, which is described in the second part of this paper, by pulling on the ventricles, and thus putting into motion a complex mechanism, determines the sequence of the auricles and ventricles.

The experiment of Stannius, described in 1852, has done more, however, toward putting physiologists on the right track than any other contribution to this subject. Stannius, it is well known, separated by means of a ligature the sinus from the auricles in the frog's heart and found that the sinus then continued to beat with undisturbed rate, whereas the subjacent parts of the heart came to rest. It was this experiment, as interpreted and built upon by Gaskell, Englemann and others, forty or more years later, that finally led to the conception that the pace-maker is a part of the heart itself, and that part, namely, the sinus region, which possesses the highest grade of rhythmicity. Before this conclusion was generally accepted, however, the view had first to be overcome that the beat of the heart is dependent on the ganglia, described by Remak shortly before Stannius reported the results of his ligature of the heart. It was Gaskell who showed that in the frog's heart rhythmicity is not located in the ganglia, but "in those parts of the heart muscle which remain least altered both in circular arrangement of their fibers and in their physiological status."

We may be permitted to recall in this connection a recently closed chapter in the physiology of the heart, because it illustrates so well the pitfalls in the path of our efforts to attach function to a likely structure. Kaiser,<sup>3</sup> in 1894, reported that if the frog's heart is brought to a standstill by tying off the sinus, a single stimulus applied to the surface of either the auricle or the ventricle is followed by only a single response, whereas if the stimulus be applied in the region of Bidder's ganglion in the auriculoventricular ring, each single stimulation is followed by a series of rhythmical contractions. He then goes on to say that "if Bidder's ganglion be removed, stimulation in the region which before aroused a series of responses now gives only one response for each stimulus." Kaiser, therefore, regarded the ganglion as the rhythmical center of the heart. Gaskell has shown since, however, that Kaiser's

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<sup>2</sup> Kurschner. Wagner's Handwörterbuch der Physiologie, Braunschweig, 1850, p. 80.

<sup>3</sup> Kaiser. See Martin, Bull. Johns Hopkins Hosp., 1905, xvi, 380.

conclusions were based on faulty experimentation. By working more carefully, Gaskell proved that Bidder's ganglion might be pierced with a needle without causing any contractions of the heart; whereas the slightest prick of the muscular tissue in the auriculoventricular groove would give rise to a series of contractions. Obviously Kaiser had stimulated the heart tissue subjacent to the ganglion, though he believed he was stimulating the ganglion only. It is hoped that subsequent sections of this paper will serve to show how closely akin to this problem and to the methods of solving it, is the problem of impulse initiation as it presents itself to us to-day.

#### ANATOMICAL

The recent impetus given to the attempts to localize a pace-maker of the heart is perhaps due more to certain recent advances in the anatomy of the heart than to any other one cause, and we must, therefore, first direct attention to the light which has been shed on our subject by the efforts of anatomists.

Of the primitive hearts, that of the eel is selected as a type, owing to the care with which its physiology has been studied, and because it seems to elucidate especially well some of the problems with which this paper deals. This heart<sup>4</sup> comprises three contractile cavities, the sinus venosus, the auricle and the ventricle. The arrangement and relations of these chambers are shown only diagrammatically in Figure 1. At the junction of the sinus with the auricle the whole circumference of the sinus wall does not terminate directly in the proper auricular tissue, for here the proper auricular tissue does not form a complete chamber, its floor being made up of what appears to be a direct prolongation of the ventral wall of the sinus. The auricle is not directly continuous with the ventricle, there is a short intervening tubular communication resembling the *canalis auricularis*. This connection is effected by means of an extremely narrow and prolonged strand of muscle fibers which is prolonged from the muscular wall of the auricular canal, and, penetrating a considerable amount of connective tissue which lies in that situation, at length becomes continuous with the muscular substance of the ventricle. The muscular continuity between the *canalis* and the ventricle is established by means of a remarkably long and slender isthmus of muscle substance which becomes continuous with the central fibers of the ventricle. In an effort to show the relation of the mammalian heart to that of the eel, Figure 2 has been evolved. We do not mean to maintain that the assumptions involved in this diagram would pass muster before a comparative anatomist. Be that as it may, the diagram has proved of great

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<sup>4</sup> McWilliam Jour Physiol, 1885, vi, 192 from which what follows is largely quoted



service in the attempt to unify the contributions to the subject of impulse initiation and conduction

Inasmuch as the sinus is the pace-maker of the cold-blooded heart, it behooves us first to determine what becomes of the sinus in the evolution of the heart to the mammalian form. The embryological method of determining this matter has been pursued by His.<sup>5</sup> His investigations have shown that in the course of development the counterpart of the sinus venosus of the cold-blooded heart becomes in the human heart the part of the right auricle which His designates the sinus reuniens.<sup>6</sup> One portion of the sinus, namely, the coronary sinus, according to His, persists as an easily distinguishable structure, the right horn of the sinus, however, sinks deep into the auricle, and the walls of these two

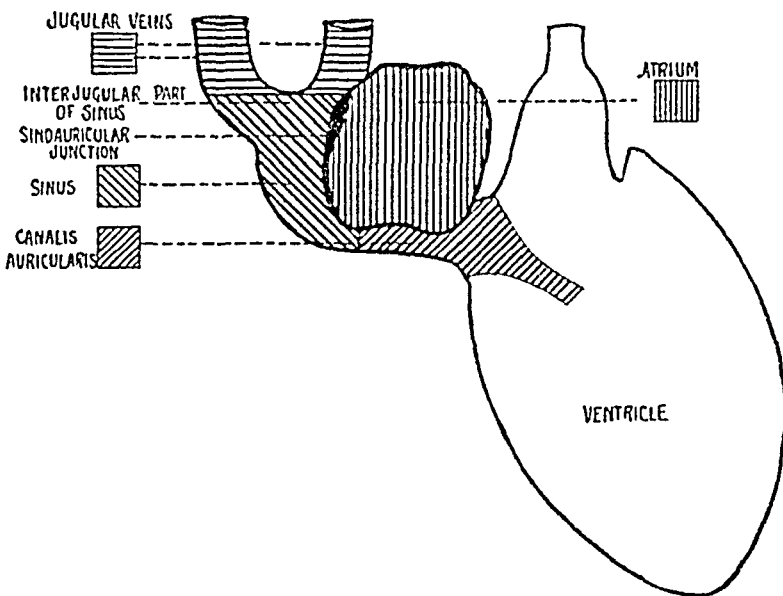


FIGURE 1

Fig 1—Heart of the eel. Diagrammatic. Modified from McWilliam

regions become fused to such an extent that anatomists, to quote, "as yet have had no occasion to designate the sinus as a definite part of the heart." Nevertheless, its limits are distinguishable at all ages. Externally it is delimited on the right by the sulcus terminalis, a groove on the surface of the heart just to the right of the opening into the auricles of the superior and inferior venae cavae. On the inner surface of the auricle corresponding with the sulcus terminalis is a ridge, the tenia terminalis. To the right of this ridge the wall of the auricle is roughened by the pectinate muscle, to the left it is smooth. This smooth part is the

<sup>5</sup> His, *Anatomie menschlicher Embryonen*, Leipzig, 1880, p. 148.

<sup>6</sup> The terms sinus reuniens and sinus venosus will be employed interchangeably.

region of the sinus venosus. By the comparative anatomical path as pursued by Keith and Flack,<sup>7</sup> the sinus in the adult mammalian heart has been found to have practically the same contour. These investigators also state that in the mammalian heart the greater part of the sinus is submerged by an overgrowth of muscular tissue of other regions. According to Keith and Flack, "two parts only are left exposed on the surface of the heart (1) the musculature of the superior vena cava, (2) the musculature of the coronary sinus."

We may therefore conclude that in the mammalian heart the remnants of the sinus venosus are to be found in an extensive area of the right auricle. Roughly, this area may be said to occupy the region between and including the superior vena cava above and the coronary

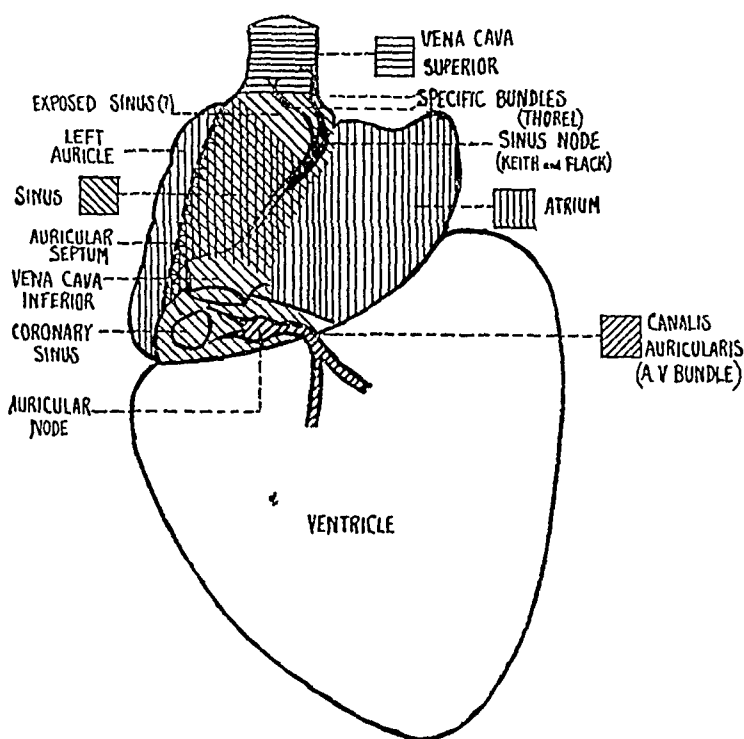


FIGURE 2

Fig 2—Mammalian heart. Diagrammatic. Figures 1 and 2 are drawn to show schematically the probable homologies of the cold-blooded and warm-blooded hearts.

sinus below, and extending from this region to the insertion of the interauricular septum into the auriculoventricular junction (Fig 2). The amount of sinus tissue persisting is not made clear, presumably but little remains.

In the same paper, Keith and Flack describe the structure now known as the sinus node or the node of Keith and Flack. This node, owing largely to the suggestion thrown out by Keith and Flack to the effect that in it "the dominating rhythm of the heart normally begins," has since assumed great prominence in the literature of the subject of impulse

<sup>7</sup> Keith and Flack. Jour. Anat. and Physiol., 1907, xli, 172.

initiation, whole volumes having already been written on it. Originally described as "numerous peculiar muscle fibers, some nerve cells and nerve fibers" surrounding the artery lying in the sinoauricular junction and located in the groove termed by His the sulcus terminalis, this node, or perhaps, the so-called specialized tissue of this region, has with further investigation assumed a more definite form, and what is of greater significance in the interpretation of the results of experimentation, has grown in extent and complexity. Thus Koch<sup>8</sup> has shown that it is club-shaped, a distinct enlargement, known as the head, sending a few fine strands back into the angle between the superior cava and the right auricular appendix, and a long tapering process downward to terminate midway between the superior and inferior cavae (Fig 2). Thorel,<sup>9</sup> on the other hand, described not alone a structure of this form, but in addition many strands beginning as loops around the superior cava, and extending downward as far as the coronary sinus (Fig 2). The fibers of the node communicate freely with the heart muscle fibers that surround it. It is important to bear in mind that the sinus node is not the sinus venosus, but is a so-called specialized tissue lying in the sino-auricular junction.

Although the discussion of the anatomy of the auriculoventricular bundle is reserved for the second part of this paper, it is necessary to state here that this structure is now believed to be a remnant of the part of the primitive heart-tube, known as the canalis auricularis, which unites the sinus venosus with the ventricle.<sup>7</sup> It consequently should be termed the sinoventricular instead of the auriculoventricular bundle.

#### PHYSIOLOGICAL SECTION

##### GENERAL LOCALIZATION IN THE MAMMALIAN HEART

In the past the study of the heart beat in cold-blooded animals has been of inestimable service in the elucidation of the functions of the warm-blooded heart. Experience of many years has shown that practically all of the findings obtained from the study of the former can be applied with but slight modification to the latter. Such knowledge of the site of normal impulse initiation as we have gained from observation of the cold-blooded heart should, therefore, be of service to those who are now concerned with this problem as it applies to the warm-blooded heart. In cold-blooded animals the beat starts in the great veins above the point where they unite with the sinus venosus, or if not there, certainly not below the sinus venosus.<sup>10</sup> In view of the picture by Keith

8 Koch. *Med Klin*, 1911, No 12.

9 Thorel. *Verhandl d deutsch path Gesellsch*, 1910, p 71.

10 Meek and Eyster. *Am Jour Physiol*, 1912, xxxi, 31.

and Flack indicating that in the turtle's heart there is at the sinoauricular junction a collection of tissue which closely resembles the sinus node of higher animals and seems to be its homologue, we wish to lay special stress on the fact that the beat of the turtle's heart does not begin in the sinoauricular junction. Just what becomes of the great veins in the evolution of the heart has not, so far as I am aware, been determined. Presumably they become incorporated with the sinus in the wall of the right auricle. We should, therefore, expect the beat of the mammalian heart to begin in the right auricle in the region of the sinus venosus, or in the veins opening into it; not at the sinoauricular junction.

#### RHYTHMICITY OF THE RIGHT AURICLE

Attention has already been called to the observation of Nysten to the effect that the right auricle is the part of the heart of man that longest preserves its irritability to the constant current, and that for a long time this region was known to be the *ultimum moriens* of the body. That the right auricle is the most rhythmical part of the mammalian heart can be demonstrated in a striking manner by severing functionally the right auricle from the rest of the heart, but leaving its nutritive connection with the heart for the most part undisturbed. When this is done the right auricle invariably beats more rapidly than the rest of the heart.<sup>11</sup> When the functional separation is not quite complete a partial block may develop, every other or every third beat of the right auricle determining a beat of the rest of the heart.<sup>12</sup> It is of interest in this connection that the left auricle, when severed from the rest of the heart by the same method, usually ceases to beat at once and definitively. It is therefore obvious that the part of the heart in which the sinus venosus lies buried, normally determines the beat of the heart.

#### EXACT LOCALIZATION IN MAMMALIAN HEART

##### GENERAL REMARKS

In considering the efforts directed toward a more exact localization of the site of impulse initiation reference may at once be made to the view, which now is widely considered a demonstrated fact,<sup>13</sup> that the sinus node of Keith and Flack is the normal pace-maker of the heart. At the very beginning of the discussion of this subject we wish to call attention again to certain *a priori* considerations that are opposed to this view. The sinus node lies in the sinoauricular junction, if it is

11 Fredericq Acad roy de Belg Bull de la cl sc, 1901, p 126, ref Arch internat de physiol, 1912, xii, 109, Erlanger and Blackman Am Jour Physiol, 1907, xix, 125

12 Erlanger and Blackman Am Jour Physiol, 1907, xix, 125

13 See, for example, Howell, Text-Book of Physiology, Phila, 1911, Ed. 4, p 529

the pace-maker it would therefore follow that in the mammalian heart the beat begins in this junction. This, we have seen, is not the case in lower forms. It should be borne in mind, however, that the last word has not yet been said with regard to the anatomy, or better perhaps with regard to the homologies of the sinus node. According to Koch's latest description, the node in the dog is two or more centimeters long, while Thorel claims that the so-called specialized tissue of this region is not confined to the sinus node of Keith and Flack, but occurs in a rather extensive area, an area, it would seem, that is almost coterminal with the sinus region (Fig 2). If the latter view should prove to be correct, then to say that impulse initiation is localized in the specialized tissue is tantamount to saying that it is localized in the sinus. However this may be, in the attempts to determine whether or not the sinus node is the normal pace-maker, practically all investigators have had before them the node as pictured by Koch.

#### INSPECTION

The first effort toward a more exact localization of impulse initiation in the warm-blooded heart was made by McWilliam<sup>14</sup> in 1888. McWilliam observed that, in the dying heart, spontaneous contractions begin either just at the point of union of the great veins with the heart, or in the wall of the veins a short distance above this point. The same method of observation in the hands of other investigators has yielded a somewhat similar result. Thus in the dying heart of the rabbit, Hering<sup>15</sup> found that contraction waves may start in the region of the mouths of the two superior cavae, and in the dog's heart<sup>16</sup> usually at the mouth of the superior vena cava, occasionally, however, at the mouth of the inferior vena cava. Fredericq<sup>17</sup> finds that in the dog the impulse starts in the right auricle between the two cavae. I have often watched for the spot from which the last or the first impulse starts in the dying or reviving heart, respectively, of mammals,<sup>12</sup> but have never succeeded in making a finer localization than to the region of the great veins as a whole. Finally Koch has concluded from observations on the hearts of still-born human fetuses that the beat starts in the coronary sinus. It is, therefore, obvious that inspection of the heart certainly locates the site of impulse initiation in the region of the sinus venosus, possibly nearer to the superior than to the inferior cava. A finer localization by this method does not seem to be possible. It should be borne in mind, however, that the logic of this method of determining the normal cardio-motor area is not entirely clear. It serves to locate the most viable parts

14 McWilliam *Journ Physiol*, 1888, ix, 167

15 Hering *Pflüger's Arch f d ges Physiol*, 1900, lxxxii, 21

16 Hering *München med Wehnschr*, 1909, lvi, 845

17 Fredericq *Arch internat de physiol*, 1906, iv, 60

of the heart, not those possessing the highest rate of rhythm, which, after all has been said, is *the* property that determines the seat of origin of the contraction wave

RHYTHMICITY OF DIFFERENT REGIONS OF THE RIGHT AURICLE AS DETERMINED BY EXCISION AND BY STRIPS

The above-mentioned experiments show that the most highly rhythmical portion of the heart is the right auricle. Are all parts of this region equally rhythmical, or are certain parts more rhythmical than others? By excising in various ways various parts of the auricles of the perfused cat's heart and noting the effect on the heart rate, it was shown<sup>12</sup> in 1907 that the region of the great veins probably possesses the highest grade of rhythmicity, but that the rhythm of this region exceeds but little that of the coronary sinus region. It was pointed out, however, that this method is open to the objection that the cuts, by altering the distribution of the perfusion fluid to the several parts of the auricles, might have altered the rhythmicity of neighboring parts. Three years later it was discovered that strips of the cat's, rabbit's and dog's auricle, when excised, placed in a bath of Locke's solution, and occasionally stimulated tetanically, would give a beautiful series of beats, and for hours, provided, however, that the strips contained tissue from that region of the right auricle which approximately coincides with the sinus reuniens of His.<sup>18</sup> These experiments furnish further evidence in favor of the view that the beat is initiated in the sinus region. But what is of greater significance to the present discussion is the observation made by the aid of this method that the regions of the superior vena cava, of the inferior vena cava and of the coronary sinus possess approximately the same grade of rhythmicity. Within the last few months this observation has been completely confirmed by Moorhouse,<sup>19</sup> who, in addition, has controlled his experiments by exactly localizing the sinus node by means of serial sections. His experiments show in a striking manner that a strip containing the sinus node as compared with strips made from the auricle just below the node or just posterior to the node, is far from exhibiting a constant predominance of rate.

Furthermore, it has been found that stimulation of auricular strips frequently is followed by an acceleration of the rate of their beat.<sup>12</sup> Such an acceleration is obtained, however, only when the part of the strip stimulated is from the sinus region of the heart. In their analyses of the functions of the various parts of the cold-blooded heart, Gaskell, Engelmann, McWilliam and others, lay the greatest stress on this reaction of heart muscle to stimulation, maintaining that it is characteristic

18 Erlanger Am Jour Physiol, 1910, xxvii, 87

19 Moorhouse Am Jour Physiol, 1912, xxx, 358

of highly rhythmical tissues. However this may be, it cannot be without interest that in the mammalian heart this response is obtained, not alone from the region of the sinus node, but from the whole of the sinus region.

#### EVIDENCE FURNISHED BY ACTION OF DRUGS ON STRIPS

Inasmuch as a great deal of stress is laid in this paper on evidence furnished by strips of the auricles beating in Locke's solution, it is of prime importance to prove that such evidence is valid. In the case of the cold-blooded heart, strips have for many years been employed for the purpose of determining the properties of the various parts of the heart, and of interpreting the response of the heart to stimuli of all kinds. So far as I am aware, all of the material thus obtained has been accepted by physiologists without question as applying to the whole heart. Nevertheless we must be prepared to show that mammalian strips do react as does normal heart muscle. Moorhouse is now engaged in an effort to gather evidence bearing on this question. His main method is to study the behavior of strips when bathed in Locke's solution to which various of the so-called heart drugs are from time to time added. Although this research is not yet completed, it has proceeded far enough to justify the statement that the strips containing sinus tissue respond exactly as does the whole heart to drugs which are supposed to act on muscular tissue as well as on the nervous tissue. Of the latter group, nicotine, which is supposed first to stimulate and then to paralyze the terminals of pre-ganglionic fibers (inhibitory fibers here) first inhibits and subsequently accelerates the strips just as it does the whole isolated heart. Pilocarpin, which slows the whole heart presumably by stimulating the vagus terminals in the heart muscle, also slows the strips, and this action can be prevented as in the whole heart by atropin. Atropin given alone causes the well-known acceleration by paralyzing the vagus terminals, and epinephrin causes the usual acceleration, presumably by stimulating the accelerator terminals in the muscle. Of the drugs whose prime action presumably is on muscular tissue, all that have been tried, namely, caffeine, the digitalis group and aconite, increase the rate of the beat and the tone of strips as well as of the whole heart. There can be no doubt, therefore, that the auricular strips behave like perfectly normal intact auricles.

Great emphasis has been laid by all writers who have dealt with the histology of the nodes, on the presence in them of what is termed *specialized* tissue. The nodes have peculiar histological characteristics, which are designated "embryonic." It is assumed by many of these writers that "embryonic" tissue is more rhythmical than other heart tissue, and that consequently the nodes are the motor centers of the heart. Now to come to the point, if this tissue is specialized in the direction of rhythmicity, the sinus node, or the strip containing it,

should not alone be more rhythmical than companion strips containing no nodal tissue, which we have seen is not the case, but in addition it should show a *specialized* response to the heart drugs. It has been found by Moorhouse, however, that if there is any difference at all in the behavior of the strips toward the drugs above mentioned, it is in the direction of greater rhythmicity on the part of the companion sinus strips, not the nodal strip. We may, therefore, conclude with the statement that if it should eventually be proved that the sinus node is the motor center of the heart it would not have this function by virtue of its rhythmical properties.

#### SIGNIFICANCE OF SLOWING AND STOPPAGE FROM EXCISION OF THE SINUS REUNIENS

Another method extensively employed in the effort to localize the pace-maker of the heart has been to determine whether or not there is a definite and fixed area, excision of which invariably stops the heart, or permanently slows its rate. The interesting results that this method has yielded have usually been applied to the problem in hand without bearing in mind all of the possibilities in the case. It is appreciated that the most plausible explanation of loss of activity following removal of a part of an organ is that the part removed determines that activity. Nevertheless, this is by no means the only explanation, it is conceivable, for instance, that such a removal may result in the establishment of a block between a region of high and of low rhythmicity under which circumstances the latter region, as is well known, will temporarily stop beating and then, after the awakening of its inherent rhythmicity, begin to beat again, though more slowly than before. It is also conceivable that as a result of injury or of partial removal, the function of the parts remaining may be altered or annulled temporarily for reasons that at present are not entirely clear. The central nervous system offers interesting and familiar examples of temporary loss of activity in parts not directly injured or removed. Thus, immediately after the onset of hemiplegia, all of the underlying reflexes are abolished, the paralysis is flaccid, soon, however, the reflexes return and the paralysis then becomes spastic.

The heart itself offers a familiar instance of the wide-spread, and at present inexplicable, effect of local injury or stimulation. It is a well-known fact that momentary stimulation of any point on the auricles or on the ventricles may throw the whole of the corresponding chambers into fibrillation. It has been shown by Garrey<sup>20</sup> that this continued incoordination is not due to any influence emanating primarily from the site stimulated. For if the area that was stimulated be excised while

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20 Verbal communication



fibrillation is continuing, the incoordination of the heart does not stop, whereas the area excised, namely, the one that was stimulated, may at once cease to fibrillate

With this analysis in mind we may review first the results on the rate of the heart beat of excision of the sinus region and of the sinus node. Excision of the whole sinus region is in effect the first ligature of Stannius, by which the sinus of the frog's heart is functionally separated from the rest of the heart. In this experiment, it will be recalled, the sinus continues to beat, whereas the subjacent parts cease beating for some time. When eventually the distal parts begin to beat it is usually with normal sequence and a slow rate. It is obvious that, owing to the complete fusion of the sinus with the auricle, the exact repetition of this experiment is not possible in mammals. For to remove all sinus tissue would involve removing practically all of the right auricle, with the exception of the appendix and neighboring tissue, down to and including the beginning of the auriculoventricular bundle. The Stannius experiment has, however, been approximated in mammals. In 1907 it was shown<sup>11, 12</sup> that in the dog's heart *in situ* clamping off of all of the region of the great veins with a specially devised clamp may result in a temporary stoppage of the heart, and occasionally perhaps a persisting slight slowing of the heart rate. In the perfused heart it was shown that excision of this region frequently, although by no means invariably, results in transitory stoppage of the parts of the heart below it, which, after recovery, usually beat at a permanently slowed rate.<sup>21</sup> These experiments were performed before the node of Keith and Flack was described, there is not the slightest doubt, however, but that the sinus node was invariably included in the tissue removed. It happens not infrequently that this operation is followed by the disappearance of the as-vs pause, the auricles and ventricles contracting synchronously instead of in sequence. But of this particular subject more later.

#### RESULTS OF EXCISION OF THE NODE

Since the node was described in 1907, attention has been directed to the effects of removing the region containing it alone, as compared with the removal of other regions. The results reported seem to be most inconstant. Flack,<sup>22</sup> one of the discoverers of the node, and Jager,<sup>23</sup> experimenting with the dog's and cat's hearts *in situ*, report totally negative results when the nodal region is excised or destroyed by heat. These experiments were carefully controlled by histological examination.

21 This result differs materially from that previously reported by Langendorff and Lehmann (Arch f d ges Physiol, 1906, 111, 352) but has been abundantly confirmed by others.

22 Flack Arch internat de physiol, 1911, 1, 111

23 Jager Deutsch Arch f klin Med, 1910, c, 1

Magnus-Alsleben<sup>24</sup> also reports totally negative results in the perfused heart of the rabbit. Lohmann<sup>25</sup> applied formaldehyd solution to the region of the node and obtained a slowing of the heart rate. It is scarcely necessary to call attention to the obvious difficulty of localizing the effects so produced. Brandenburg and Hoffmann<sup>26</sup> have attempted the isolation of the nodal region by means of cold. They state that when this region is thus isolated there is always a sudden change in the rate and sequence of the heart beat. Their article is, however, full of statements which scarcely can be reconciled with their conclusions. For instance, they state that injury to the auricles may cause other parts of the auricles to become the pace-maker. One is inclined to ask the question: Does this not provide them with a means of accounting for exceptions to the rule? It is for the purpose of avoiding injury to the auricles that they use cold to isolate the various regions of the auricles, despite this fact, they find that if the sinus node be isolated on three sides of a quadrangle by means of cuts, cooling of the node still causes the changes in rate mentioned above. Why, one might ask, do not the parts of the auricle injured by the cuts in this case now determine the beat of the heart?

Quite recently Cohn and Kessel,<sup>27</sup> working with the perfused dog's heart, stated in a preliminary note that the last of four cuts removing a rectangular area containing the sinus node always causes stoppage with subsequent slowing, or at least subsequent slowing of the auricles, which never regain their former rapidity, that when the excision of the node is incomplete no change in rate results. They consequently conclude that the node is the pace-maker of the heart. In view of the obvious differences between these results and those obtained by myself working with Blackman, the experiments of Cohn and Kessel were repeated with certain modifications by Moorhouse.<sup>19</sup> Moorhouse studied the reaction of the perfused dog's heart after excision of two rectangular strips, one (a) containing the sinus node, the other (b) immediately below this, but still a part of the sinus reuniens. Fifty experiments in all were made, all with the greatest of care and with exacting controls. Inasmuch as the results obtained were almost identical in the case of strips (a), and (b) the conclusion was reached that there is a balance of rhythmical power through the caval portion of the sinus region. The nodal region is not more rhythmical than neighboring regions of the sinus reuniens.

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24 Magnus-Alsleben *Arch f exper Pathol u Pharmacol*, 1911, **lxiv**, 228

25 Lohmann *Arch f d ges Physiol*, 1908, **cxxiii**, 628

26 Brandenburg and Hoffmann *Med Klin*, 1912, **viii**, 16

27 Cohn and Kessel *THE ARCHIVES INT MED*, 1911, **vii**, 226

The final report of Cohn, Kessel and Mason<sup>28</sup> then appeared. It profoundly modified their preliminary statement, in that positive results, namely, stoppage and slowing of the auricles, were obtained in but 80 per cent to 90 per cent of the experiments. Notwithstanding these negative results they still are of the opinion that their experiments prove the sinus node to be the pace-maker of the heart. In view, however, of the fact that exactly the same results are obtained and just as frequently when a square of tissue below the sinus node is excised as when a square of tissue containing the sinus node is excised, experiments of this kind cannot be said to prove the specificity of the sinus node in the matter of impulse initiation.

#### EVIDENCE FROM WARMING AND COOLING

Another method that has been used for the purpose of locating the pace-maker of the heart has been to determine the area, warming or cooling of which will alter the rate of the whole normally beating heart. This method was first employed in the study of the mammalian heart by McWilliam<sup>24</sup> in 1888. McWilliam states that "the application of slight heat locally to the terminal part of the vena cava superior gives a very marked acceleration in the rhythm of the whole heart. A similar slight local heating of the ventricular apex or any part of the ventricular substance gives no change in cardiac rate." No further details are given, so that the reader is left to infer whether or not McWilliam tested the effect of temperature on other parts of the auricles than the superior vena cava. However this may be, McWilliam's final conclusion is that in the cat and the dog the usual origin of contraction is in the venous wall. In 1905, Adam,<sup>29</sup> working in Langendorff's laboratory, reinvestigated this subject and found that localized moderate warming and cooling altered the heart rate only in an area lying between the mouths of the two cavae and extending in the form of a triangle to the base of the auricle. The most sensitive spot lay between the two veins, somewhat nearer to the lower. Now, after the discovery of the sinus node, the same method in the hands of Ganter and Zahn<sup>30</sup> reveals that the nodal region, as delimited by Koch, alone is sensitive to temperature changes, the region overlying the thickest part of the node being the most sensitive spot. Brandenburg and Hoffmann<sup>26</sup> have obtained practically the same results. Ganter and Zahn and Brandenburg and Hoffmann, of course, conclude that the node is the normal pace-maker. The former investigators suggest a curious hypothesis to account for their observation that one part of the node may be more sensitive than others. It is

28 Cohn, Kessel and Mason. *Heart*, 1912, III, 311.

29 Adam. *Pflüger's Arch f d ges Physiol*, 1906, cxi, 607.

30 Ganter and Zahn. *Pflüger's Arch f d ges Physiol*, 1912, cxlv, 335.

obvious, therefore, that the method of warming and cooling also gives results that seem inconstant. By it the rate of the heart may be affected over the terminal portion of the superior cava, over the node and near the inferior cava. The results are, however, consistent in this respect, namely, that they have been obtained only within the limits of the sinus reuniens. Those who have employed the temperature method have overlooked one consideration which may prove to be of considerable importance, namely, the accessibility of the region of the sinus reuniens to the thermodes employed. Both His and Keith and Flack<sup>7</sup> explicitly state, it will be recalled, that in the mammalian heart nearly all of the sinus recedes from the surface of the heart. To say the least, it is a rather remarkable coincidence that in the hands of recent investigators only the two regions that presumably remain at the surface of the auricles are affected by moderate temperature changes.

#### EVIDENCE FROM ELECTROCARDIOGRAPHIC STUDIES

Lewis<sup>31</sup> has recently shown that the action current of beats of the auricles of the dog's heart determined by electrical stimulation of various points on the surface of the auricles resembles in form the normal action current only when the point stimulated is in the vicinity of the sinus node. This observation is considered as almost final proof that the impulse normally starts from the sinus node. The interpretation of Lewis' results, however, is not as simple as it may seem. It is necessary to bear in mind, for instance, that possibly this is one of the regions where primitive sinus tissue appears on the surface of the auricles. Is it not also possible that the impulse is so conducted through the auricle, owing either to the existence of definite paths, or to the thickness of the tissue, which in the region of the sinus node is comparatively great, that the sinus node region becomes negative electrically before other parts of the auricles? But there is still another possibility which an analysis of Lewis' results seems almost to substantiate.

The discussion of this possibility is begun with the assumption that the impulse which causes the heart to beat starts in the sinus venosus and crosses the sinoauricular junction into the auricles at the most accessible point. Reference to the diagram (Fig. 2) shows that this point is just about where the sinus node lies. Now the amplitude of electrical changes associated with activity is largely dependent on the mass of tissue reacting. The sinus venosus in the cold-blooded heart is relatively large, yet even when the electrodes are placed directly on it the deflection shown by the string galvanometer is relatively small. Samoiloff,<sup>32</sup> for instance, does not seem to picture a sinus action current

31 Lewis, *Heart* 1910-11, 23.

32 Samoiloff, *Pflüger's Arch. f. d. ges. Physiol.*, 1910, **xxxv**, 417.

in his extensive study of the frog's heart. The sinus of the mammalian heart probably contains much less tissue relatively than that of the cold-blooded heart. The action current of the former should consequently be correspondingly smaller. It is, therefore, not surprising that as yet no one has obtained a wave on the electrocardiogram of warm-blooded animals assignable to activity of the sinus.

Bearing in mind these assumptions an analysis of Lewis' results reveals the following. In all cases in which the contraction was evoked by a stimulus placed immediately over the sinoauricular junction (sinus node) or anywhere on the superior vena cava side of it, the P wave obtained, that is, the wave of auricular activity, closely approximates the P wave of the normal heart beat. In other words the curve is normal when it is started at the place where the impulse normally enters the auricle, or at some point on the sinus above this place. It is abnormal when it is started on the auricle or possibly on the sinus below the point at which it normally enters the heart. Lewis' experiments indicate, therefore, that the impulses pass into the auricle by way of the sinoauricular junction, they do not force us to the conclusion that the sinus node is the pace-maker.

The foregoing discussion also might serve to account for the observation of Lewis, Oppenheimer and Oppenheimer<sup>33</sup> and of Wybauw,<sup>34</sup> that as a rule the point on the auricle first to become electronegative lies approximately over the region of the sinus node. For if the tissue of the sinus is small in amount, and for the most part submerged in the surrounding tissue, the point first to become negative would be the place where the impulse passes from the sinus into the auricle. It should also be mentioned that the points of primary negativity, as determined in these two investigations, do not exactly coincide. Furthermore, both record exceptions to the rule. These exceptions the authors consider of no significance. Yet to us it is obvious that if the sinus node has the specific function of starting the beat of the heart it should be possible to show that under normal circumstances it invariably performs this function. This the electrocardiographic studies have failed to demonstrate.

#### SIGNIFICANCE OF NODAL RHYTHM

We have thus far purposely omitted the discussion of a result very commonly obtained in experiments on the sinus region of the auricles, namely, a change in the sequence of the auricular and ventricular beats. This change consists in a shortening of the auriculoventricular interval, or, more usually, in the actual disappearance of this interval, the auricles and ventricles contracting at almost exactly the same moment. The

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<sup>33</sup> Lewis, Oppenheimer and Oppenheimer. *Heart*, 1910-11, 11, 147.

<sup>34</sup> Wybauw. *Arch. internat. de physiol.*, 1910, x, 78.

term nodal rhythm has been applied to this type of beat. It may appear suddenly or, occasionally, gradually after operations on the sinus region of the heart. It is assumed by those who consider the nodes of Keith and Flack and of Tawara the most highly rhythmical regions of the heart, that the synchronous a-v beat is the result of the usurpation by the auricular node of the function of setting the pace of the heart when the more highly rhythmical sinus node is excised. Inasmuch as the tissue of the auricular node resembles somewhat that of the sinus node, this change in the character of the beat is considered clear proof of the specialization of the so-called nodal tissue in the direction of rhythmicity. The argument leading to this conclusion, it will be seen, is based on two propositions, namely, first, that the removal of the sinus node always results in the transfer of impulse initiation to the auricular node, and, second, that during the so-called nodal rhythm the impulse starts in the auricular node. Neither of these propositions has as yet been proved. The first proposition is by no means a fact.

It is true that extensive removal of auricular tissue, such, for example, as the liberal excision of much of the tissue in the sinus region in the perfused heart<sup>12</sup> very frequently is followed by synchronous contractions of the auricles and ventricles. But simple excision of the sinus node alone rarely results in the appearance of nodal rhythm, and even when it does occur it may be only transitory, the normal or almost normal sequence often returning after a longer or shorter period of nodal rhythm. Nodal rhythm was but rarely seen in the experiments of Jaeger, Flack, Magnus-Alsleben, Cohn and Kessel, Moorhouse, etc. On the other hand, it is claimed that the abolition of the functional activity of the region of the sinus node by means of cold almost invariably produces nodal rhythm. One cannot help but feel, however, that the temperature effects were not as nicely localized as it is believed they were. Be that as it may, a perusal of the reports of these experiments shows clearly that removal of the sinus node by cold does not always result in nodal rhythm. Thus Ganter and Zahn<sup>20</sup> state that "after stopping the activity of the sinus node by means of cold the auricles and ventricles do not always beat exactly synchronously. The as-vs interval may have a positive or negative value." While Brandenburg and Hoffmann<sup>26</sup> state that occasionally after removing the sinus node by cold or by excision the synchronous beats of the auricles and ventricles may be transitory, and that the original normal sequence may again return.

But even if it be admitted for the purpose of argument that the auricular node is determining the beat of the chambers while they are beating synchronously, it would by no means follow that the auricular node normally is more rhythmical than all the rest of the super-ventricular parts with the exception of the sinus node. Might not the

nodal rhythm be due to a temporary loss of the reactivity of the whole of the auricles, temporary inhibition, if that term is preferred, resulting from the tampering with the auricles, and that until the auricles recover, the auricular node, or, better, the next lower heart segment, determines the heart beat. It may be added that with the return of the normal sequence it can be shown that the auricles are setting the pace, since further operations on the auricles, such as cutting<sup>35</sup> or cooling the region of the coronary sinus<sup>36</sup> many again change the sequence. It is not entirely irrelevant to add, in this connection, that auricular strips containing the auricular node are not nearly so rhythmical as strips made from other parts of the auricle not alone while the sequence is normal, but even when, as a result of the excision of the great veins, the chambers are beating synchronously. Thus a companion strip from the coronary sinus region made at such a time always beats faster than the strip containing the auricular node.

Neither has it been proved that during so-called nodal rhythm the auricular node invariably is setting the pace of the heart. Indeed, almost the only observation in favor of this view is the fact that the chambers beat approximately simultaneously,<sup>36</sup> whereas there is just as good evidence to show that at such times the sinus may still be setting the pace of the whole heart. It has just been mentioned that extensive excision of the region of the great veins in the perfused rabbit's heart often results in so-called nodal rhythm. In ten consecutive experiments in which this occurred the auriculoventricular bundle was cut with a pair of scissors. The scissors were inserted through the opening made by the excision of the veins, one blade on either side of the exposed auricular septum down into the ventricles. A cut thus made in a heart as small as the rabbit's must undoubtedly have injured the node of Tawara. Yet this cut never slowed the auricles, indeed it usually left their rate entirely unchanged, the ventricles on the other hand showed the slowing that usually follows section of the bundle of His. Be this as it may, there is no necessity for limiting explanations of the so-called nodal rhythm to the view that it can be produced only by impulses arising in the auricular node. Indeed, inspection of the progress of the contraction wave in cooled hearts at a time when as a result of liberal excision of the great veins the auricles and ventricles are beating synchronously, has frequently revealed another cause. It can be seen in such experiments that the contraction wave may start in the region of the coronary sinus, and travel so slowly through the neighboring tissues of the auricles that the distant auricular appendices contract quite as late as the ventricles. Reference

35 Zahn *Zentralbl f Physiol*, 1912, xxvi, 495

36 Brandenburg and Hoffmann and Ganter and Zahn state that cooking or warming the auricular node after excision of the sinus node changes the rate of the beat.

to Figure 2 indicates clearly how a cut of this kind by forcing the impulse to travel for a long distance through the auricular canal before it can gain access to the auricles might lengthen the sinoauricular pause and so cause it to approximate the auriculoventricular pause

Another question suggests itself here, namely, if it is admitted that the only two parts of the auricles that have sufficiently high rates of rhythm to dominate the rhythm of the auricles are the sinus node and the auricular node, how is the fact to be explained that the change from the auricular type of beat to the auriculoventricular type frequently is gradual, the auriculoventricular pause shortening slowly until the two chambers finally beat together?

#### STOPPAGE FROM INCISION OF THE NODE

Finally, a word with regard to the significance of stoppage of the heart from incision of the node. In 1907, Hering<sup>37</sup> stated that a simple incision in the sulcus terminalis, which presumably involved the sinus node, stopped completely the beat of the supraventricular parts. This result was at once hailed by Keith and Flack as proof of their suggestion that the sinus node is the pace-maker of the heart. In the same year<sup>12</sup> attention was called to the fact that stoppage of the heart often follows operations on or sometimes even a mere touch anywhere on a rather large area of the auricles, and the view was then expressed that stoppage probably occurs only when the part stimulated is at the time determining the beat of the heart. Irrespective of what may be the fate of this suggestion, it is interesting to note that recent work<sup>38</sup> has completely failed to confirm Hering. Incision of the node in the perfused heart of the dog does not stop the heart, to the contrary, it accelerates the heart rate.

## II LOCALIZATION OF CONDUCTIVITY IN THE HEART

### HISTORICAL

In the historical introduction to the first part of this paper reference was made to the earliest hypotheses that were advanced to account for the sequence of the auricles and ventricles. We will, therefore, confine our attention here to the development of our modern ideas with regard to the dependence of the ventricles on the auricles. It has been said that Kurschner, in 1850, suggested a very complex explanation of the dependence of the ventricles on the auricles. One part of this explanation is of more than passing interest with reference to the topic in hand. "It is," Kurschner says, "now generally assumed that the musculature of the auricles is completely separated from that of the ventricles. From a study of the tissue composing the valves, I encountered conditions

37 Hering *Pflüger's Arch f d ges Physiol*, 1907, cxvi, 143

38 See, for instance, Cohn, Kessel and Mason, etc



which are opposed to this view, I found muscle fibers extending from the auricle over into the valves" In attempting to account for the sequence of the heart beat he then proceeds to say

The anatomical conditions of the heart are indeed such that a measurable interval of time can elapse between the contraction of the auricles and of the ventricles The muscle fibers which pass from auricle into the venous valves contain the organic basis of this phenomenon They cannot contract without supplying a stimulus to the ventricles The contraction of the auricles must, therefore, determine the contraction of the ventricles

Obviously, Kurschner might be said to have been the first investigator to have shown that "the musculature of the auricles is not completely separated from that of the ventricles" There are, however, two all-important differences between Kurschner's point of view and the accepted point of view of to-day Although the valve musculature is described by Kurschner as extending over the auriculoventricular junction, it is not in the location of the connecting muscle band, as we now know it, nor does the valve musculature fuse with the musculature of the ventricles

Over a quarter of a century later, in 1876, we find recorded what has developed into the second claim to the demonstration of the crossing of the musculature of the auricles into the ventricles In that year Paladino<sup>39</sup> wrote as follows:

The muscle layer of the sinus or auricle where it reaches the level of the auriculoventricular orifice loses the external circular layer of fibers, which stop, and is continued by the longitudinal fibers and the middle circular fibers downward to the interior of the valve leaflets Of these fibers, the longitudinal terminate in the tendons of the second and third order *And some tendons pass directly upon the walls of the ventricles, where by means of flattened muscle bundles, which are inserted upon the valve leaflets, they break up into small tendons*

In 1910, Paladino, on the basis of passages similar to the one quoted above, pleads to have his name connected with that of the discoverer of the auriculoventricular bundle, as having demonstrated a muscular connection between the auricles and ventricles As a matter of fact, a few authors have actually heeded this plea It is obvious, however, that the criticism we have applied to Kurschner's work applies with equal force to the work of Paladino,<sup>39, 40</sup> no discrete definitely localized bundle is described, but rather scattered bundles in the valves, and there is no fusion of muscle bundles with the musculature of the ventricles

In 1892-3, there appeared two articles by Kent,<sup>40</sup> which seem to represent the first of the recent attempts to determine whether or not the musculature of the auricles and of the ventricles are completely separated

39 Paladino Arch ital d biol, 1910, lxx, 47

40 Kent Proc Physiol Soc Nov 12, 1892, and Jour of Physiol, 1893, xiv,

by connective tissue Owing to the existence of some difference of opinion as to the exact significance of Kent's work in the development of this subject,<sup>41</sup> his results will be given as nearly as possible in his own words. In the adult animal (rat) a ". . . connecting sheet of muscle . . . is met with over a considerable area of the a-v groove; thus it may be mentioned that frequently in a single coronal section the connection may be seen between the outer (left) wall of the left ventricle and the left auricle, between the septum ventriculorum and the auricle, and between the right wall of the right ventricle and the right auricle" Describing a coronal section passing through the *junction of the left auricle with the left ventricle* of the heart of the newly-born rat, Kent says:

at about the center of the isthmus<sup>42</sup> the auricular fibers are seen to sweep freely down into the substance of the ventricular wall "In the young rabbit of two days old auricular fibers are seen sweeping down to the outer side of the fibrous ring, and become continuous with bundles belonging to the ventricular system The connection also exists on the right side of the heart . . . and also in the septum to the right side of the ring bearing the mitral valve" In the monkey "the fibrous ring has attained a very perfect development and it is only here and there that places can be found to show the passage of muscular fibers across the groove

#### ANATOMY OF THE AURICULOVENTRICULAR BUNDLE

In 1893, His called attention to the existence in the heart of a number of mammals of a single muscle bundle located in the posterior part of the septum and extending across the auriculoventricular junction obliquely from above and behind, downward and forward In a review written in 1899, His<sup>43</sup> correctly refers to the bearing of Kent's work on his in the following terms:

In man, indeed in mammals in general, a layer of connective tissue grows in between the muscle walls of the ventricles and auricles and separates these parts almost completely Nevertheless muscle fibers have been found in this layer (Stanley Kent) and I myself have demonstrated a bundle present in mammals as well as in man, which passes from the posterior wall of the right auricle down to the ventricular septum

While the existence of this single bundle, now usually and correctly designated the bundle of His,<sup>47</sup> has since been abundantly confirmed, the more recent work by Humblet, Retzer, Breanig, Tawara, etc., has added much to His' original description Much more, although not enough yet, is now known of its origin in the auricles, of its mode of determination in the ventricles and of the histology of its various parts Overlooking

41 Meltzer Med Rec, New York, 1909, May 22, p 873; also Nov 27, p 914

42 It should be noted that the term "isthmus" as used here could not and was not by Kent intended to be synonymous with septum, since the section is from the junction of the left auricle with the left ventricle Compare with Meltzer, loc cit. note 41

43 His Deutsch Arch f klin Med, 1899, lxxv, 316

for the present certain details on which opinion is as yet divided, the system connecting the auricles with the ventricles may be described briefly as follows

It begins in the auricle in the posterior part of the septum, just above the auriculoventricular junction, and just anterior to and in the floor of the coronary sinus. Some authors describe a very close connection between the node and the auricular tissue. According to Cohn,<sup>44</sup> for example, it would seem that there is a general transition of auricular fibers into the characteristic nodal fibers. The number of fibers forming the connection, however, varies. "There may be a great many, closely packed together, the strands separated by masses of connective tissue, or there may be but a few rather thinner fibers with only delicate connective tissue strands between." The node of Tawara, into which these strands flow, is composed of characteristic branching and anastomosing cells which possibly were seen by Kent. Beyond the node the bundle, now compact and slender and taking on the characteristics of Purkinje cells, crosses the auriculoventricular junction and, continuing its course downward and forward, comes to lie on the upper edge of the muscular septum of the ventricles where it joins with the membranous part. The subsequent course of the conducting system is probably familiar to all. It can be best and indeed strikingly demonstrated by means of the injection method of Lhamon.<sup>45</sup> Lhamon has shown that when a colored injection fluid is forced through a hypodermic needle into the conducting system it will, owing to the connective tissue sheath, remain in that system and flow even into its ultimate branches. It is thus possible to make very evident the division of the main bundle into two limbs, a right and a left, the subendocardial course of these limbs down the respective sides of the ventricular septum, their branching into secondary twigs, some of which pass by way of the false tendons cross the cavities of the ventricles to the papillary muscles, and their further branching into an anastomosing network, the ultimate fasciculi of which dip down into the myocardium, and gradually change into fibers of the ventricular type the individual fibers eventually terminating in a most interesting way in the conical point of a fasciculus of heart muscle.

Comparative anatomy and embryology, too, have added much to the significance of the His-Tawara system. Keith and Flack, in 1907, showed that in the simplest form of vertebrate heart a portion of the auricular canal, that part of the heart which in primitive forms joins the sinus with the ventricle, extends down into, or is invaginated into the ventricles. This invaginated part forms an isolated layer beneath the auriculoventricular valves. It is assumed in the primitive mammalian

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<sup>44</sup> Cohn. *Heart*, 1909 10, 1, 172

<sup>45</sup> Lhamon. *Am Jour Anat*, 1912, xiii, 55

heart that complete muscular connection between the auricles and ventricles exists around the whole auriculoventricular junction. As we ascend the animal scale, however, the invaginated portion of the auricular canal is encroached on more and more by the growth of connective tissue, until there is left only a small part of this musculature, it forms the auriculoventricular bundle. However, in certain animals, the rat, for example, auricular and ventricular fibers appear to come into close apposition in other places, especially in the right lateral auriculoventricular region. This, Keith and Flack venture to suggest, represents "one of the connections described by Stanley Kent. This close apposition, however, cannot be looked on as a connection, the auriculoventricular bundle is to be regarded as the sole connection between the auricular canal and the ventricle."

Mall<sup>46</sup> has studied the development of the auriculoventricular bundle in human embryos. At very early stages (embryo 3.9 mm.) the auricular canal forms a complete muscular connection between the sinus and the ventricle. Soon, however, as the result of the formation of subendocardial cushions of connective tissue, this ring becomes separated into a number of bundles, amongst which can be recognized at this time one occupying the same position and course as the auriculoventricular bundle in the adult. "The additional strips," Mall says, "may be of significance in view of Romberg's and Kent's observation." Kent found such bundles in the left wall of the heart as well as in the right wall in rats and rabbits. It is possible that some of these strips may be constant, or they may be variations. "At any rate," he goes on to say, "their presence has not been established as has the atrioventricular bundle of His." The auriculoventricular bundle, consequently, is not a structure of recent development, rather, it is a part of the wall of the primitive tube from which the heart is evolved. This fact, as has been said, should have some weight in inferring the function of the bundle from its structure, despite the great changes in, and the apparent complication of, the adult mammalian heart, it still preserves its primitive arrangement.

#### PHYSIOLOGY OF THE AURICULOVENTRICULAR BUNDLE

Considering now the physiological aspects of the problem of localizing conduction from auricles to ventricles in the warm-blooded heart, the view which held sway previous to 1893 practically universally was that the correlation of the work of the auricles and ventricles was affected through nerves crossing the auriculoventricular junction. An excellent idea of the point of view held by the physiologists of this period may be conveyed by a quotation from an article by Tigerstedt<sup>47</sup> in which are

<sup>46</sup> Mall *Am Jour Anat*, 1912, xiii, 284

<sup>47</sup> Tigerstedt *Arch f Physiol*, 1884, p. 497

recorded the results of severing completely by means of a cut the connection of the auricles with the ventricles in the rabbit's heart. In order to make this quotation clear, it should be preceded by the statement that in the previous year Wooldridge<sup>48</sup> had accomplished the same separation by means of a mass ligature, with the result that the auricles and ventricles contracted independently of each other. Tigerstedt says.

Wooldridge in dogs and cats performed the experiment of severing the *nervous connection* [italics ours] between the auricles and ventricles, that is to say he made the Stannius experiment on the warm blooded heart.

And again, by way of introduction to his experiments Tigerstedt says. The interesting results obtained by Wooldridge by means of his ligature made it necessary to repeat with more rigorous methods the separation of the *nervous connections* [italics ours] between the ventricles and auricles because it might be objected that the ligature failed to divide all of the nerve fibers between the auricles and ventricles.

This assumption seemed justifiable in view of the prevailing opinion that there was no muscular connection between the auricles and ventricles.

In the same paper in which Kent described muscular connections in various parts of the auriculoventricular junction, mention is made of some experiments in which a clamp was applied to the auriculoventricular groove of the mammalian heart just as Gaskell had done in the frog's heart. Kent states without giving the records "that almost precisely similar results [to those of Gaskell] were obtained." It may, therefore, be assumed that he obtained with this clamp the various stages of partial and complete block. The experiments of Wooldridge, Tigerstedt and Kent, therefore, demonstrate conclusively that in the mammalian heart the impulse which causes the ventricles to beat arises in the auricles and crosses the auriculoventricular junction, the old view that the sequence is due to stimulation by the blood is disproved. Shortly after His<sup>49</sup> described the muscular bundle that bears his name, he read before the Physiological Congress a paper describing the results of cutting this bundle. No final report of these experiments has ever appeared, and it was not until the bundle of His was redescribed in 1904 by Retzer, by Breaunig and by Humblet that the attention of physiologists was attracted to this structure. Then Humblet<sup>50</sup> showed, as had been shown by His, that section of practically nothing but the bundle in the perfused heart results in complete dissociation of the auricles and ventricles. A year later the same observation was made by Hering,<sup>51</sup> also in the perfused heart. Simultaneously the results were published of compressing in a specially devised clamp practically nothing but the His bundle in

48 Wooldridge Arch f Physiol, 1883, p 522

49 His Zentralbl f Physiol, 1895, ix, 469

50 Humblet Arch internat d physiol, 1904, c, 278

51 Hering Pflüger's Arch f d ges Physiol, 1905, cvii, 97

the heart *in situ* <sup>52</sup> The results thus obtained were similar to those following compression in a clamp of all of the auriculoventricular junction in both cold and warm-blooded animals. These results have since been abundantly confirmed. Practically the only conflicting evidence comes from the Bern laboratory. Lomakina<sup>53</sup> says that dissociation of the auricles and ventricles can be obtained by dividing the superficial macroscopic nerves in the auriculoventricular groove. This result has not been confirmed. Paukul<sup>54</sup> and Kronecker<sup>55</sup> state that crushing the auriculoventricular bundle in rabbits does not block the passage of the impulse into the ventricles. Cohn and Trendelenburg<sup>56</sup> have offered what seems to be a plausible explanation of this anomalous result. They have found that in the rabbit the bundle may not pass into the ventricle as a single strand, but may divide into several strands which spread out after the fashion of a fan. They suggest that some of these branches probably escaped inclusion in the ligature as placed by Paukul and Kronecker. We are, therefore, justified in asserting that experiments of the kind thus far described prove that the only *functional* connection between the auricles and ventricles is by way of the His bundle.

It is not, however, unreasonable to maintain that other connections exist, such, for example, as were described by Kent, that under ordinary circumstances such other connections are dormant, and that in the course of the few hours the heart is under observation in experiments as ordinarily performed these connections cannot develop their activity sufficiently to perform vicariously the function of the His bundle. This objection seems to be met by those instances of chronic heart-block in man, in which a lesion, more or less accurately limited to the region of the auriculoventricular bundle undoubtedly has served to block permanently the passage of the excitation wave through the auriculoventricular junction. Nevertheless, clinical observations, even when confirmed by post-mortem findings, do not carry the conviction of a clean-cut experiment, there is always the possibility that tissues other than those found to be diseased may be the seat of pathological processes which, however, have escaped detection. This objection has been removed by some experiments in which heart-block was produced by crushing under aseptic precautions the auriculoventricular bundle in the clamp above alluded to and then allowing the animals (dogs) to live <sup>57</sup> Two of these animals survived the operation 320 and 313 days respectively. During this entire period there was complete dissociation of the auricles and

52 Erlanger, *Zentralbl. f. Physiol.*, 1905 xix, 9, also *Jour. Exper. Med.*, 1906, viii, 8.

53 Lomakina: *Ztschr. f. Physiol.*, 1900 xxxix, 377.

54 Paukul: *Ztschr. f. Physiol.*, 1908 li, 177.

55 Kronecker: *Brit. Med. Jour.* 1910 i, 135.

56 Cohn and Trendelenburg: *Pflüger's Arch. f. d. ges. Physiol.*, 1910 cxxxi, 1.

57. Erlanger and Blackman: *Heart* 1910, i, 177.

ventricles. We may conclude, therefore, that there is no connection between the auricles and ventricles that can vicariously assume the functions of the bundle of His. Thus the path of conduction across the auriculoventricular groove is narrowed down to the auriculoventricular bundle.

Now that we know that the auriculoventricular bundle is as much a part of the primitive heart tube as any other part of the heart, we could scarcely expect conduction in it to differ from conduction in the rest of the heart, the presence in the bundle of a considerable amount of nerve tissue to the contrary notwithstanding.<sup>58</sup> Nevertheless, the question has been asked, Is it possible to carry further the localization of impulse conduction in this region by determining whether it is through muscle or through nerve? The results of experimentation in this direction, though suggestive, are still far from being conclusive. The fact that in animals regeneration of function does not occur even in the course of a year after complete section of the auriculoventricular bundle, would seem to indicate that nerves are not concerned with the process of impulse conduction. This conclusion is based on the usually accepted view with regard to the power of regeneration of heart muscle and of nerve. Wounds of heart muscle heal by the formation of scar tissue, the muscle cells show little, if any, tendency to regenerate.<sup>59</sup> On the other hand, it is well known that in due time nerves will regenerate. This is true not alone of nerve trunks, but also of nerve plexuses, such, for example as the mesenteric plexus.<sup>60</sup>

When our attention was first directed to this subject a perusal of the literature revealed that regeneration of nerve and of muscle, in so far as it pertains to the heart, had been studied by histological methods only. So far as could be ascertained, no effort had been made to determine whether restoration of conductivity across a healed wound of the heart will occur. Consequently the attempt was made to determine whether a functional connection between the auricles and ventricles could be established by uniting contiguous surfaces of the auricles and ventricles, which have been denuded of their epicardial covering. This attempt failed. It was not, however, considered conclusive because of the great difficulty of obtaining close apposition of thin-walled auricle to ventricle. For the purpose of putting this question of regeneration to a crucial test, the following experiment was then made:<sup>61</sup>

Under aseptic precautions the tip of the auricular appendix of the dog's heart was crushed in a clamp so as to sever it functionally from the auricle proper excepting a narrow strip along one edge. The tip was not completely isolated, since it was feared that then atrophy of the functionless part would occur and

58 Wilson: *Anat. Rec.* 1902, viii 262

59. See Thorel: *Lubarsch and Ostertag's Ergebnisse* 1903, ix, 861.

60 Meak: *Am. Jour. Physiol.* 1910, xxv 267.

61 Erlanger *Am. Jour. Physiol.* 1902 xiv, 375

would interfere with the interpretation of the results. The animal was then allowed to live some 130 days. Then the tissue of the auricle was crushed in a line extending out to the tip of the auricle and intersecting at right angles the old line of crush. By this procedure the appendix is divided into two triangular areas, one separated from the heart by the old and new lines of crush, the other still functionally connected with the heart through the undestroyed isthmus at the edge of the auricle. By using the second area as a control, it was then found that functional connection between the first area and the heart had not developed. Histological examination revealed that heart muscle had not grown across the old contusion, whereas nerve could be traced from one side to the other. The presence of this nervous union obviously did not suffice for the conduction of the impulse.

Such a result makes it very probable, although it does not prove, that the muscular rather than the nervous elements of the His bundle carry the impulse from the auricles to the ventricles. In support of this conclusion it might be added that Cullis and Dixon<sup>62</sup> have shown that the application of a 5 per cent solution of cocaine to the bundle of His does not produce heart-block, although all of the nerve fibers with which the cocaine comes into contact would certainly be paralyzed.

We have yet to consider conduction within the ventricles. Is the impulse delivered by the His bundle to the ventricular musculature at or near the point where it crosses the auriculoventricular junction, or must it first traverse the entire complicated system described by Tawara, DeWitt, Lhaman and others?

These questions were first formulated only a few years ago and are still the subject of discussion. The experiments devised to answer them are as yet but little beyond the formative stage. Considering first the results of cutting both of the main divisions of the bundle of His, the general statement may be made that the mass of evidence points to a union of the bundle fibers with the ventricular musculature below the bifurcation. Thus Barker and Hirschfelder<sup>63</sup> have shown in the dog that cutting the left branch usually gives complete block. In the one case in this series of experiments in which block did not appear, both the ventricles seemed to contract coordinately. Eppinger and Rothberger<sup>64</sup> state that cutting one limb produces an obvious effect at once, the two ventricles seem to alternate. Complete block, however, did not follow section of one limb, but only section of both. The difference in the results of these two investigations is probably merely one of degree. The experiments of Biggs, though, are not in harmony with either of the foregoing researches. Biggs<sup>65</sup> finds that in the rabbit, section of all branches of the bundle of His does not cause heart block and he furthermore finds, as do also Cullis and Dixon, working with the same animal, that retrograde conduction may sometimes occur after section of the

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62 Cullis and Dixon. *Jour. Physiol.* 1911, xli, 156.

63 Barker and Hirschfelder. *THE ARCHIVES INT. MED.*, 1909, iv, 192.

64 Eppinger and Rothberger. *Centralbl. f. Physiol.*, 1911, xxiv, 1055.

65 Biggs. *Brit. Med. Jour.*, 1908, i, 1419.



bundle This result leads one to suspect either that these investigators failed to cut all of the branches of the bundle, despite the fact that both seem to have been aware of the variations that occur in the bundle of the rabbit's heart, or that the auricles were stimulated mechanically by the ventricles, as Cullis and Dixon seem inclined to believe So far as present purposes are concerned the results, however, indicate that the termination of the His bundle lies some distance beyond its bifurcation

How much farther on its course into the ventricles does the impulse remain in the conducting system? Tawara is of the opinion that the impulse is carried in the bundles to the most distant parts of the ventricles, indeed, to the papillary muscles first The moment of contraction of the papillary muscle, it might therefore be suspected, should serve to throw some light on this question Do they contract before, with or after the body of the ventricles? Until quite recently it was regarded as probable that the papillary muscles contract synchronously with or possibly a moment later than the body of the ventricles<sup>66</sup> The reinvestigation of this subject that has been stimulated by the suggestions of the anatomists has as yet led only to conflicting results,<sup>67</sup> which need not be reviewed here

It has thus far been assumed that the secondary branches of the His-Tawara system, which, as has been said, are composed of Purkinje tissue, carry the impulse through the ventricles This assumption is based on anatomical observations and on the observation, to which reference has just been made, that section of the His bundle, or of its two main branches, produces heart block In view of the possibility of misinterpreting the results so obtained, it was thought that it would be interesting to have some definite information with regard to conduction in the ventricular portion in the His-Tawara system The first attempts in this direction seem to have been made by Hering<sup>68</sup> He cut the auriculo-ventricular bundle in the dog and then stimulated the cut surface More recently Cullis and Dixon applied electrodes directly over the intact bundle in the rabbit's heart While the results obtained in both of these researches indicate that the bundle responds to direct stimulation, the very close proximity of the ventricular musculature, which could not have been more than 1 mm away from the electrodes, renders the conclusions somewhat uncertain

It has been said that some of the branches of the His-Tawara system cross the cavities of the ventricles by way of the false tendons or inter-ventricular bands The studies of Petersen, which were confirmatory of Miss DeWitt's observations, demonstrate that some of these interven-

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66 For a discussion of this subject see Shafer's Text Book of Physiology, London, 1900, 11, 10

67 Saltzmann Skand Arch, 1908, xx, 233, Hering Pfluger's Arch f d ges Physiol, 1909, cxxvi, 225

68 Hering Pfluger's Arch f d ges Physiol, 1910, cxxxi, 572

tricular bands in the beef's heart consist of Purkinje fibers and connective tissue exclusively. Thus the way was opened to a conclusive reply to the question of irritability and conductivity in the Purkinje system. It has been determined in the perfused beef's heart that stimulation of false tendons, which were found by subsequent histological examination to be entirely free of heart muscle proper and to contain as irritable structure only Purkinje tissue, causes a contraction of the ventricles<sup>69</sup>. There could be no question in these experiments of an escape of the current to the ventricular musculature, since often the electrodes were applied to the false tendons a centimeter or more from their insertion into the ventricular wall, while the strength of the stimulus eliciting a reply from the false tendon in many cases did not suffice to elicit a reply when applied directly to the ventricular wall.

This method has also served to shed some light on other important matters. By means of it, it has been found possible to show that impulses carried to the ventricles by way of the His-Tawara system are not of necessity delivered first to the papillary muscles. If a false tendon be divided near its middle and the two stumps be stimulated separately, the ventricles will, in both cases, contract. Assuming that in both cases the impulse is delivered to the papillary muscles, the distance it must travel by way of the papillary stump of the false tendon would be much shorter than the distance by way of the septal stump, and we should expect to find a corresponding difference in the latent period of the ventricular contraction. As a matter of fact, however, the latencies have, as nearly as can be determined, the same duration.

However this may be, it can be shown that the central stump of the false tendon probably does not terminate close to its insertion into the septum. It is well known that practically all of the main branches of the His bundle lie immediately under the endocardium, the terminal branches alone apparently dipping into the depths of the myocardium. It, therefore, seems justifiable to assume that a cut a couple of millimeters deep circumscribing the septal insertion of a false tendon severs all of the Purkinje tissue connected therewith, excepting that of the terminal branches. Such a cut has been found to annul the response of the ventricles to stimulation of the circumscribed false tendon, while the mere ringing of an area of heart muscle does not of itself annul the irritability of the enclosed area. At least two interpretations of this result are possible. (1) Either the immediate connections of the false tendon with the subjacent heart tissue are not extensive enough to carry the impulse, that is to say, a relatively complete block results from the operation, or (2) the impulse before it is delivered to the myocardium, must first be carried to some distant point by the large subendocardial

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<sup>69</sup> Erlanger. *Am Jour Physiol* 1912 **xx** 395

strands of the conducting system. It remains for future work to settle this matter.

Another point of some interest in connection with the localization of conduction is the following. It is well known that impulses are conducted in either direction between the auricles and ventricles. Consequently it should be possible to show that the conducting system, if properly so-called, will carry impulses in either direction. Experiments with false tendons have shown not alone that this is the case, but also that the impulses are carried at the same rate in either direction.

### CONCLUSION

The first conclusion one is apt to draw from a review of the work that has been done in the effort to localize the site of impulse initiation and conduction is that the former subject at least is in a state of hopeless confusion. I venture to predict, however, that when the last word has been said, the structure and function of the mammalian heart will be found to be almost identical with the structure and function of the heart of cold-blooded animals, of which the heart of the eel, owing to its simplicity and to the care with which it has been studied, may serve as a type. The normal sequence of the eel's heart differs in no wise from that in other hearts, sinus, auricles and ventricles contracting in the order given, which is also the order of the rhythm of these parts when isolated. Under the eye it can be seen that the contraction begins in the venous part of the sinus. It passes from the sinus directly into the nearest part of the auricle and then spreads over the auricular tissue, whence it passes into the auricular canal through which it finally involves the central fibers of the ventricle. "The rhythmical power of each segment of the heart varies inversely as does the distance from the sinus." The auricular canal, which might almost be regarded as a prolongation of the sinus tissue, possesses a much higher rhythmical power than the auricles. Therefore, in the mammalian heart we should expect the rhythmicity of the sinoventricular bundle to be exceeded only by that of the sinus region, and this seems to be the case. In the eel's heart the impulse normally reaches the ventricle by way of the auricle, but it can reach the ventricle directly by way of the auricular canal also. In the latter event the auricles do not contract. The anatomical possibility of this path has been all but worked out in the mammalian heart. It is believed that the finding of such a path would help materially toward accounting for the appearance of nodal rhythm following excision of the upper part of the sinus region as well as for many other of the phenomena noted in this paper. In any event, we cannot afford, in the interpretation of the functions of the heart of man, to ignore the results of investigation in the field of comparative physiology.

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## A STUDY OF VASOMOTOR REFLEXES ELICITED BY HEAT AND COLD FROM REGIONS DEVOID OF TEMPERATURE SENSIBILITY (IN AN UNUSUAL CASE OF POST- TYPHOIDAL NEURITIS)

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This study was undertaken with two objects one clinical, the other physiological. From both aspects the results obtained seem to be of sufficient interest and utility to warrant their publication. The clinical object was primarily to throw light, if possible, on the diagnosis of a case which seemed to present considerable difficulty and concerning which very different conclusions had been arrived at by competent clinical observers. The physiological object was to contribute something to the solution of the question whether the afferent fibers through which the vasomotor reflexes induced by the application to the skin of heat and cold are identical with the fibers concerned in the corresponding sensations, a question which, so far as we are aware, has not received a definite answer. It is, of course, known that actual consciousness of the sensations is not necessary for the development of the vasomotor reactions, since they occur also in sleep. But we do not know whether a lesion, especially a peripheral lesion, which completely blocks the transmission of impulses along the nerves of temperature sensation, or at least prevents them from rising to the threshold value necessary for the production of sensation, blocks at the same time all the afferent vasomotor impulses set up by heat or cold. An answer to this question is not only of physiological interest, but also might, in certain cases, prove of diagnostic importance, particularly in affording a basis for an objective test of the existence and possibly for an objective measure of the acuity of temperature sensibility.

The vasomotor reflexes in this study were investigated by means of the method of measuring the blood-flow, previously described by one of

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us<sup>1</sup> The reflexes elicited in one hand when the other hand or a portion of it is placed in cold or warm water, that is to say, the contralateral vaso-motor reflexes, were preferred for this study to the ipsilateral reflexes induced in the hand immersed in the hot or cold water, since it

TABLE 1—RESULTS OF CALORIMETER TESTS ON R E

April 26, 1912 R E Hands in bath at 1 51½ p m Hands in calorimeters at 2 03 p m  
3,015 cc water in each Examination made in hospital

Time	R	L	Notes	Time	L	Notes
02	31 00	30 76		2 42	30 99	
04	30 91	30 69	Room 24 5 C	2 43	31 025	
05	30 90	30 67		2 44	31 05	Room 24 0 C
06	30 88	30 65		2 45	31 095	
07	30 86	30 63		2 46	31 12	Here cold water was brought into
08	30 84	30 63		2 47	31 13	room and excited his appre-
10	30 82	30 61	Room 24 3			hensions
11	30 80	30 59		2 48	31 15	At 2 48 right hand and wrist put
13	30 78	30 57		2 49	31 17	into water at 8 C He feels it
15	30 77	30 555	Room 24 25 C	2 50	31 19	very cold on wrist, but not at
17	30 76	30 545		2 51	31 20	all on fingers Feels fingers
19	30 75	30 55		2 52	31 205	somewhat numb
21	30 77	30 59	Room 24 2 C	2 53	31 21	
22	30 775	30 605		2 54	31 215	
23	30 78	30 61		2 55	31 215	Still feels the right wrist very
24	30 79	30 635				cold
25	30 795	30 655		2 56	31 22	The cold water is now at 12 5 C
26	30 80	30 675		2 57	31 215	Room 23 6 C
27	30 805	30 70		2 58	31 225	
28	30 81	30 725	Room 24 0 C	2 59	31 225	
29	30 82	30 73		3 00	31 23	
30	30 83	30 745		3 01	31 235	
31	30 84	30 765		3 02	31 24	Room 23 6 C
32	30 86	30 79		3 03	31 25	At 3 03 right hand and wrist put
33	30 875	30 825		3 04	31 255	into water at 43 C The wrist
34	30 885	30 835	Right hand and wrist put in	3 05	31 27	still felt cold for a little time in
35		30 85	water at 43 C Feels it	3 06	31 29	the warm water
			on wrist	3 07	31 305	
		30 865		3 08	31 32	
		30 875		3 09	31 325	
		30 895		3 10	31 325	
		30 915		3 11	31 325	
40		30 93		3 12	31 325	At 3 12 took hand out of calor-
41		30 965				imeter
				3 25½	31 17	The right hand is reddish, ob-
						viously fair vasodilatation Tem-
						perature of R 30 395 C

Cooling of R 0 49° in 51½ minutes Cooling of L 0 155° in 13½ minutes Volume of right hand 379 cc, of left 397 cc Rectal temperature 37 05 C

is commonly stated that even in the absence of connection with the central nervous system the blood-vessels quickly regain the power of responding to local changes of temperature through the intervention of a local

1 Heart, 1911, III, 33, 76, THE ARCHIVES INT MED, 1912, IX, 706

regulating mechanism Thus Trotter and Davies,<sup>2</sup> who studied the phenomena following the section of cutaneous nerves in themselves, state that "The vasomotor changes which follow nerve-section begin to show a diminution within a few days of the operation, and by the end of six weeks scarcely any abnormality of this function can be detected It seems probable, therefore, that recovery occurs by some local compensatory mechanism rather than by an active regeneration of the vasomotor nerve fibers"

TABLE 2—RESULTS OF CALORIMETER TESTS ON R E

May 2, 1912, R E Hands in bath at 3 15 p m Hands in calorimeters at 3 26 p m Mouth temperature 36 57 C Temperature of arterial blood at wrist (say) 36 6 C Examination made in hospital

Time	R	L	Notes	Time	R	Notes
3 24½	31 10	31 16	Room 25 5 C	3 45	31 235	At 3 43 left wrist withdrawn
3 27	31 07	31 15		3 46	31 27	feels warmth only on middle ph
3 28	31 09	31 16		3 47	31 305	anx of left index finger Hand ke
3 29	31 095	31 17		3 48	31 345	thus for the rest of the experimen
3 30	31 105	31 185	Room 25 4 C	3 49	31 395	Room 24 9 C
3 31	31 105	31 20		3 50	31 41	At 3 50 left hand put in cold wat
3 32	31 11	31 21		3 51	31 45	at 8 3 C Wrist not immerse
3 33	31 11	31 225				Only feels cold on middle phala
3 34	31 12	31 225	At 3 37 left hand put in water at 43 C Room 25 4 C He feels warmth on wrist	3 52	31 47	Room 25 0 C
3 35	31 125	31 23		3 53	31 48	Still feels cold intensely on midc
3 36	31 125	31 23		3 54	31 495	phalanx of index The cold wat
3 37	31 135	31 225		3 55	31 505	is now at 10 4 C
3 38	31 13		At 3 40 withdrew wrist, dried it, and put in cloth to keep it from vessel	3 56	31 52	Still complains of cold in th
3 40	31 14		Now feels warmth only on middle phalanx of left index finger	3 57	31 525	phalanx
3 41	31 15		At 3 42 left wrist immersed He feels it warm	3 58	31 535	Hands out at 3 58
3 42	31 155			4 09	31 425	Temp of L is now 30 95 C
3 43	31 175					
3 44	31 195					

Cooling of calorimeters R 0 11° in 11 minutes L 0 275° in 32 minutes Volume of right hand 361 cc, left hand, 385 cc Pulse 76 (half reclining)

## REPORT OF CASE

*History*—The patient first came under observation of one of us in 1898, when he showed very marked atrophy of the small muscles of the hands with less atrophy of the extensor group of the forearms and legs He was not under close observation then until 1908, when the following history and condition were elicited

R E white, aged 44 years, widower, laborer

*Family History*—Father died at the age of 57 of "paralysis of the brain" Mother died at the age of 30 of "childbirth" Three sisters and three brothers

<sup>2</sup> Trotter and Davies Jour Physiol, 1909 xxxviii, 188

dead, four died when very small, one died of typhoid fever and one died as the result of an accident. One uncle died of tuberculosis. Grandfather died of "liver trouble."

*Previous History*—The patient had scarlet fever, measles, and mumps when small, had typhoid fever twenty-four years ago (in 1884), rheumatism in left shoulder two or three years previous to examination, and again a slight recurrence in the right leg during the previous seven months. The patient denies ever having had any venereal disease, had much catarrh sixteen years previously, could not smell anything unless very strong for the previous ten years. Had cough and expectoration for the previous five or six years. Tubercle bacilli were found in the sputum twice. He had pleurisy several times two or three years prior to examination, and was short of breath for five or six years, ankles swollen some six years previously, appetite only fair, some vomiting after eating for the previous year or so, pain in stomach at times—cramp like, yet not very sharp, bowels regular, no incontinence of feces, some incontinence of urine eight or nine months previously that lasted for three months, had had no incontinence lately, no slowness in urination, and no change in sexual function. The patient experienced unsteadiness in the dark for twenty years, also when he closed his eyes to wash his face. There was some double vision for previous six years, no paresthesia. Wasting of hands, arms and legs, first noticed about the knees followed typhoid fever twenty-four years previously. He noted loss of sensation in hands, then in feet three or four years after he noticed the muscular wasting. He had fourteen operations for empyema of the frontal sinuses. When he had typhoid fever he had pain in the right groin, no bed sores, hair came out, noted much muscular wasting while sick, could not walk for three months after getting over his typhoid, had no pain in legs or arms at that time. Wasting of muscles was very marked three years after typhoid and about this time he noted loss of sensation, first in the lower legs, then in the feet, and then in the arms and hands. Feet numb, no stinging or burning. At this time the urine and sputum showed nothing abnormal.

*Physical Examination*—This showed scars over the frontal sinuses from repeated operation, which interfered with the action of the frontal muscles, no pupillary reaction to ordinary light, no nystagmus, some contraction of the field of vision in all diameters, jaw-jerk not present, no glandular enlargement, no changes in the bones or joints, no scars or pigmentation of the skin.

*Muscular System*—Quite marked atrophy of the trapezius, supraspinatus and also of the serratus magnus on the right side, some wasting of the serratus magnus on the left. Both erector spinae muscles rather small and wasted. Considerable strength in the biceps, triceps and deltoid on both sides, also of the supinators and pronators, very marked atrophy of all of the small muscles of the hands and extensors and flexors of the forearm. Ulnar border of forearms concave due to muscular atrophy. Marked atrophy of the thenar and hypothenar eminences. He could not "make a fist" with either hand and had practically no grip. The face had a somewhat mask like appearance, probably due to the sinus operations. He had a double partial ptosis (due to sinus operations?), was able to shut both eyes, there seemed to be no paralysis of the facial muscles and the orbicularis oris was strong. The muscles of the soft palate and tongue were normal. The voice was husky, more like a voice of weakness than of paralysis. Platysma myoides and sternocleidomastoid and other muscles of the neck were much atrophied. The pectoral muscles showed good volume. The abdominal muscles were greatly weakened so that he could not bring himself into a sitting position without the aid of his arms. The atrophy was more marked on the left side. There was considerable wasting of all groups of muscles of the thigh, especially the abductors, marked atrophy of the peroneal groups, causing toe-drop, fairly good power in the calf muscles, extensors and flexors practically without power, marked wasting of the interossei, had some flat-foot.

*Reflexes*—Bicipital, elbow and wrist-jerks all absent. Abdominal reflex present at all levels, cremasteric absent. Knee jerks and Achilles jerk absent on

TABLE 3—RESULTS OF CALORIMETER TESTS ON R E

May 8, 1912 R E He says he feels better and is in better spirits than at the two previous examinations, partly due to the fact that his wife accompanied him, also to the expectation of some pecuniary reward Examination made in laboratory Hands in bath at 1 43 p m, in calorimeter at 1 53 p m, 3,015 cc in each Mouth temp 36 95 C

## FIRST PART OF TEST

Time	R	L	Notes	Time	R	L	Notes
1 52	30 995	30 97	Room 22 2 C	2 01	31 01	31 04	
1 54	30 935	30 925		2 02	31 025	31 05	Room 22 9 C
1 55	30 935	30 93		2 03	31 04	31 065	
1 56	30 935	30 93		2 04	31 065	31 095	
1 57	30 96	30 955	Room 22 7 C	2 05	31 095	31 125	Room 23 0 C
1 58	30 98	30 99		2 06	31 11	31 14	
1 59	30 995	31 01		2 07	31 13	31 165	
2 00	31 00	31 025		2 08	31 15	31 20	

## SECOND PART OF TEST

Time	L	Notes	Time	L	Notes
2 09	31 205	At 2 08 right hand put in water at	2 39	31 71	
2 10	31 22	43 C Wrist not immersed He	2 40	31 725	At 2 40½ right hand put in water
2 11	31 23	does not feel warmth at all	2 41	31 735	at 8 degrees Wrist carefully dried
2 12	31 235	Room 22 8 C	2 42	31 74	and not immersed He did not feel
2 13	31 25	The warm water is now at 41 C	2 43	31 75	the cold at all
2 14	31 26		2 44	31 765	Room 22 7
2 15	31 295	Room 22 95 C	2 45	31 78	
2 16	31 32		2 46	31 795	
2 17	31 325		2 47	31 805	The cold water is now at 9 7°
2 18	31 33		2 48	31 81	
2 19	31 34		2 49	31 825	
2 20	31 35	Room 22 9 C	2 50	31 83	Room 22 6
2 21	31 36		2 51	31 835	
2 22	31 38		2 52	31 835	
2 23	31 405		2 53	31 835	
2 24	31 425		2 54	31 84	At 2 54 right hand, including wrist
2 25	31 435	Room 22 7 C	2 55	31 84	put into water at 43° He feels
2 26	31 45		2 56	31 84	the wrist warm
2 27	31 47		2 57	31 84	Room 22 8
2 28	31 495	At 2 28 right hand, including wrist,	2 58	31 84	
2 29	31 50	immersed in water at 43 C Feels	2 59	31 845	
		it warm on wrist	3 00	31 845	
2 30	31 525	Room 22 9 C	3 01	31 85	
2 31	31 53		3 02	31 855	
2 32	31 54		3 03	31 855	
2 33	31 565		3 05	31 85	At 3 05 hand out of calorimeter
2 34	31 59	Room 22 7 C	3 13	31 74	Temp of R 30 39
2 35	31 625				
2 36	31 635				
2 37	31 65				
2 38	31 685	Room 22 8 C			

Cooling of calorimeter R 0 76 degrees in 65 minutes cooling of calorimeter L 0 11 degrees in 8 minutes Volume of right hand 403 cc Volume of left hand 421 cc



both sides. No plantar reflex, no Babinski, Oppenheim or Gordon reflexes were present on the left side. There was a slight plantar reflex on the right side involving but the four small toes, and with this stimulus the quadriceps contracted although he felt nothing. No Babinski, Oppenheim or Gordon present on the right side, gluteal reflexes present, no enlargement or tenderness of the nerve trunks found.

*Sensory Symptoms*—The patient was anesthetic to all forms of sensation over the frontal region laterally to the line of the outer canthus of the eyes, probably due to nerve lesions caused by sinus operations. No anesthesia of the rest of the face. No anesthesia of the neck or trunk. Toes, feet, and legs were anesthetic to all forms of sensation to above the knees. On the right side the line of anesthesia is just at the upper border of the patella and running around to one inch higher on the posterior surface. On the left leg the line of anesthesia was an inch above the patella in front, curving downward a little on each side, then curving up posteriorly to the upper part of the popliteal space. Analgesia extended to about two inches higher than anesthesia to touch in front and slightly lower posteriorly. Deep pressure sense was absent in the legs.

Left arm, hand and fingers were anesthetic to all forms of sensation from a line about three fourths inch above elbow-joint.

Right arm, hand, and fingers were anesthetic to all forms of sensation, including deep pressure, below a line about one and one-half inches above the condyle of the humerus, extending a little higher on the anterior surface.

Stereognostic sense was gone in the hands, could not tell position of fingers or hand.

Patient stood with knees over extended and walked with steppage gait, throwing right foot farther forward, however, than left. Toes had a tendency to drag, due to drop foot.

Lumbar puncture showed low pressure, clear fluid, twelve cells, mostly lymphocytes, to the count. Urine showed nothing abnormal.

April 13, 1909, the patient showed slight nystagmus, contrary to what was previously observed. Pupils equal and reacted to light and accommodation. Seemingly some weakness of the labial muscles and cheek muscles. Tongue showed wrinkling and thinning, seemingly slight atrophy, equal on both sides. Some difficulty in swallowing owing to the food coming out of the nose.

He said he could not walk down hill, but must run down owing to weakness of the extensors of the legs. At this time both patellar and both plantar reflexes were absent.

April, 1912, blood showed a negative Wassermann reaction.

May, 1912, patient again came under observation at the Cleveland City Hospital and a few additional facts in regard to the history may be added.

The patient stated that he was in a sanatorium for tuberculosis seven years previously and was discharged as seemingly cured after nine months' stay. He gave no history of lightning pains or gastric crises. He still experienced considerable difficulty in walking. He had some trouble at times in controlling the bladder and had several involuntary bowel movements, but as a rule he had no trouble in controlling the sphincters of bladder and bowel.

He said his feet felt cold and numb at times, but he had no other subjective sensory symptoms.

He had lately married for the fourth time. History of his marital relations showed nothing suggestive of a syphilitic infection.

He believed that the strength in his hands and feet was slowly improving, which seems to be very certain judging from the records of former examinations. The patient said his hands and feet always felt cold to other people when he, himself, could tell no difference.

Examination of the chest showed evidence of a quiescent tuberculosis at the right apex. Cardiovascular system shows nothing abnormal, although heart sounds seem quite faint. No murmurs present.

TABLE 4—RESULTS OF CALORIMETER TEST ON R E

May 18, 1912 R E He came from his home to the City Hospital for this examination The weather was fairly warm Hands in bath at 11 48 a m Hands in calorimeters at 11 58 a m 3,015 cc water in each Mouth temperature, 36 55 C

## FIRST PART OF TEST

Time	R	L	Notes	Time	R	L	Notes
11 57 1/2	30 91	30 87	Room 24 8 C	12 09	30 99	30 985	
11 59	30 89	30 85		12 10	30 995	31 00	
12 00	30 90	30 86		12 11	31 00	31 02	Room 24 8 C
12 01	30 91	30 88	Room 24 9 C	12 12	31 01	31 025	
12 02	30 93	30 91	He saw cold water being	12 13	31 02	31 035	
12 03	30 94	30 92	prepared with ice	12 14	31 035	31 045	Room 24 6 C
12 04	30 94	30 925	Room 24 9 C	12 15	31,045	31 055	
12 05	30 945	30 93		12 16	31 06	31 065	
12 06	30 96	30 94		12 17	31 065	31 08	At 12 17 right hand (1
12 07	30 97	30 955					wrist) put into water
12 08	30 98	30 97	Room 24 9 C				8 2 C He did not feel the cold at all

## SECOND PART OF TEST

Time	L	Notes	Time	L	Notes
12 18	31 085		12 49	31,555	
12 19	31 09	Room 24 4 C	12 50	31 575	At 12 50 immersed right hand ov
12 20	31 10		12 51	31 58	wrist in the cold water Feels
12 21	31 11	Room 24 6 C	12 52	31 59	very cold on wrist The water
12 22	31 125				8 9 C
12 23	31 14		12 53	31 585	Room 24 6 C
12 24	31 155	Room 24 5 C	12 54	31 60	
12 25	31 17		12 55	31 61	Still feels it quite cold on wrist
12 26	31 19		12 56	31 625	Room 24 6 C
12 27	31 22		12 57	31 625	
12 28	31 23	Room 24 5 C	12 58	31 625	
12 29	31 24	At 12 29 right hand (not wrist)	12 59	31 63	Room 24 7 C
12 30	31 25	put into water at 43 5 C Feels	1 00	31 63	
12 31	31 25	nothing Room 24 7 C	1 01	31 635	
12 32	31 27	The cold water is now 9 7 C	1 02	31 64	At 1 02 right hand and wrist p
12 33	31 31		1 03	31 645	into water at 43 4 C Feels
12 34	31 325	Does not feel the warm water	1 04	31 65	warm on wrist Room 24 9 C
12 35	31 34	Room 26 9 C	1 05	31 67	
12 36	31 365		1 06	31 69	Room 24 9 C
12 37	31 40		1 07	31 71	
12 38	31 42	Room 24 9 C	1 08	31 72	
12 39	31 425		1 09	31 725	
12 40	31 435		1 10	31 73	Room 24 9 C
12 41	31,445	The warm water is now 40 C	1 11	31 73	
12 42	31 46	At 12 42 right hand (not wrist)	1 12	31 735	The warm water is now at 40 3 C
12 43	31 485	put into water at 8 C Does not	1 13	31 74	At 1 13 dried and wrapped up rig
12 44	31 50	fee. the cold at all	1 14	31 75	hand
12 45	31 515	Room 24 8 C	1 15	31 755	
12 46	31 525		1 16	31 765	Room 24 9 C
12 48	31 54		1 17	31 775	
			1 18	31 79	
			1 19	31 815	
			1 20	31 825	Room 24 9 C
			1 21	31 835	At 1 21 hand removed from calor
			1 29	31 76	meter Temperature of R 30 12 C at 1 29

Cooling of R 0 64° in 72 minutes, L 0 08° in 8 minutes Volume of right hand, 391 cc, left hand 409 cc

Abdomen showed nothing abnormal Liver and spleen did not seem to be enlarged Genitalia were normal

Reflexes Knee jerks, Achilles-jerks, Babinski, Gordon and Oppenheim reflexes all absent on both sides Marked wasting of about the same muscles that were atrophied at the time of examination made in 1908, and described above, although the atrophy did not seem to be as pronounced and the strength in the hands was much better

*Special Sense*—He could taste neither sweet, sour nor bitter on the anterior two-thirds of the tongue on both sides On the posterior one third of the tongue he seemed to be able, especially on the left side, to taste acid, but no sweet or bitter substances Sense of smell was absent Hearing and sight were normal

*Sensation*—There was loss to all forms of sensation (including sense of position, deep pressure and vibratory sense) in the right hand extending up on the forearm with a U shaped boundary on the anterior surface and extending much higher on the posterior surface, but here also having an irregular boundary outline (Figs 1 and 2) Just above this area of complete anesthesia to all forms of sensation there was an area extending almost to the elbow joint where

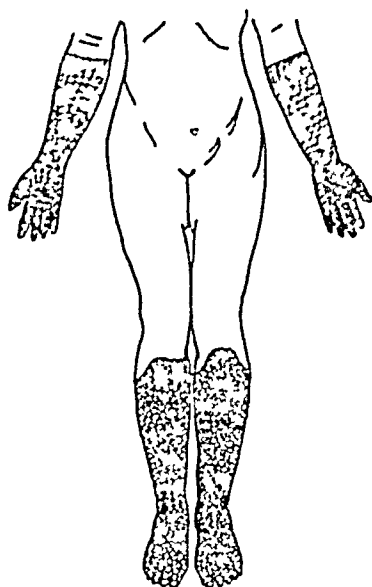


Fig 1—Anterior surface Total anesthesia indicated by shading with small circles, hypesthesia (to all forms of sensation) by shading with small crosses

all forms of sensation were present, but less acute than normal The left hand with the exception of the entire index finger was anesthetic to all forms of sensation (At the blood flow examinations he stated positively that he felt heat and cold only on the middle phalanx of index finger) The upper boundary of anesthesia of the hand was about as high as the so called glove anesthesia Above this area was a band about 5 inches wide where all forms of sensation were present, but less acute than normal Above this band there was another area extending almost to the elbow joint where all forms of sensation were again absent

The right foot and leg were anesthetic to all forms of sensation up to an irregular shaped line with its highest point three fingers' breadth below the patella Posteriorly this line curves downward to a point six finger breadths below the level of the head of the fibula Over this area all forms of sensation were lost, including muscle sense, deep pressure sense and vibratory sense The left foot and leg showed almost identically the same area of anesthesia, with practically the same boundary, with the exception that there was a small round area about an inch in diameter on the sole of the foot just below the inner malleolus where pain sense seems to be present

There was a sore on the plantar surface of the right big toe that seemed to be painful to touch. Patient thought it was caused by badly fitting shoes. It soon healed up perfectly. Numerous other abrasions due to shoes were not felt by the patient at all.

Marked displacement laterally and in other direction, of the knees, ankles and toe joints was not perceived by the patient, but he seemed to appreciate the position of the left big toe.

It seemed as though vibratory sense was lost over the patella, fibula, tibia and bones of the feet. There seemed to be a lessening of the vibratory sense over the lower third of both thighs.

*Blood Examination*—Blood examination showed 5,200,000 reds, 6,900 leukocytes and a negative Wassermann. Lumbar puncture showed rather low pressure (80 drops to the minute) clear, cell count 4 per cmm.

X-ray examination of the chest and spine showed nothing abnormal.

*Urine*—Specific gravity 1.018, trace of albumin, no sugar and no casts found.

*Electrical Reaction*—Electrical reaction showed greater diminution in the faradic than in the galvanic irritability in the areas affected by atrophy and

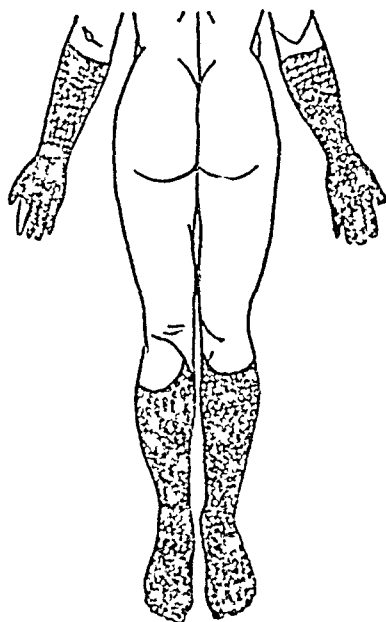


Fig 2—Posterior surface. Shading same as in Fig 1. Note the small circular area on the left sole which seems to be sensitive to pain.

anesthesia. Tested more exactly November 14, 1912, with a McIntosh battery (galvanic current from 25 cells with total voltage of 37. Faradic current from coil on the same apparatus actuated by two similar cells, No. 4 Columbia type  $1\frac{1}{2} \times 4$  inches in size connected in parallel). The patient stated that he could feel somewhat better on the hands and arms than at last examination, including heat and cold. Following are details of the electrical reactions:

RIGHT ARM GALVANIC CURRENT (BROAD ELECTRODE ON BACK<sup>3</sup>)

N. Medianus (7 cm. above wrist) KCC > ACC. No KOC. Little if any AOC.  
M. Palmaris Longus KCC fair. ACC slight. No KOC or AOC. (Fairly sharp pain at KC and some pain at AC.)

M. Supinator Longus (Palm of hand) KCC (good) > ACC, which > AOC. KCC > KOC. No contraction either with K or A at C or O. (Slight pricking pain at AC, AO and KC. None at KO.)

<sup>3</sup> The "motor points" correspond to those given by Schatzsky (Allbutt's System of Medicine 1, 454). It is not implied that the position of the points was identical in our patient nor that only the corresponding muscle or nerve was always stimulated by the current used.

TABLE 5—SUMMARY OF RESULTS ON R E

Date	Temperature C of				Vol of Hand in cc		Heat Given Off in Small Calories		Blood flow Gms per Min		Flow per 100 cc of Hand per Min		Notes
	Room	R Cal	L Cal	Air Bld	R	L	R	L	R	L	R	L	
April 26	24 0	30 82	30 69	36 6	379	397	951	1,469	12 19	18 41	3 21	4 56	For the 15 mins preceding the vasomotor test For 6 mins immediately preceding the vasomotor test First 6 mins immersion of right hand and wrist in warm water Next 8 minutes First 3 mins with right hand and wrist in cold water Next 12 minutes For 10 mins before vasomotor test First 5 mins immersion of left hand in warm water Next 8 minutes First 2 mins with left hand in cold water Next 6 minutes
		30 85	30 78				459	598	14 78	19 02	3 90	4 71	
	24 0		30 88					441		14 37		3 56	
	23 6		31 04 31 18					1,161 287		29 00 19 61		7 19 4 86	
May 2			31 22					636		10 94		2 71	
	25 4	31 10	31 19	36 6	361	385	541	578	10 93	11 87	3 03	3 08	
	25 4	31 14					237		9 64		2 67		
	24 9	31 28					1,150		30 02		8 31		
	25 0	31 44					271		29 18		8 08		
		31 55					423		15 51		4 29		

May	9	22 9	31 04	31 06	36 95	403	421	1,213	1,107	12	19 00	22 12	4 71	5 25	For the 12 mins preceding vasomotor test
		22 9		31 27					867	10		16 96		4 03	First 10 mins with only anesthetic part of right hand in warm water
		22 9		31 41					1,012	10		20 29		4 82	Next 10 minutes
		22 8		31 52					329	4		16 83		4 00	First 4 mins immersion of right wrist also in warm water
		22 8		31 03					1,009	8		26 33		6 25	Next 8 minutes
		22 7		31 78					686	8		18 42		4 37	First 8 mins immersion of anesthetic part only of right hand in cold water
		22 7		31 83					282	5		12 24		2 90	Next 5 minutes
		22 8		31 85					460	9		11 13		2 64	For 9 mins immersion of right hand and wrist in warm water
May	19	21 8	30 98	30 97	36 55	391	409	1,158	1,317	18	12 83	14 57	3 28	3 56	For 18 mins preceding the vasomotor tests
		21 9	31 02	31 02				630	719	10	12 66	14 44	3 24	3 53	For the last 10 mins of this period
		21 6		31 11					383	6		13 04		3 19	First 6 mins immersion of anesthetic part of right hand in cold water
		21 6		31 19					524	6		18 10		4 42	Next 6 minutes
		21 9		31 35					1,116	13		18 83		4 60	For 13 mins during immersion of anesthetic part of right hand in warm water
		21 8		31 52					650	8		17 94		4 38	For 8 mins immersion of anesthetic part of right hand in cold water
		21 7		31 61					616	12		11 54		2 82	For 12 mins immersion right hand and wrist in cold water
		21 9		31 67					410	5		18 67		4 56	For the first 5 mins immersion of right hand and wrist in warm water
		21 9		31 73					308	6		11 83		2 89	For the next 6 mins of immersion in the warm water
		21 9		31 79					598	8		17 44		4 26	For 8 mins with right hand dried and wrapped up

## LEFT ARM GALVANIC CURRENT (BROAD ELECTRODE ON BACK)

N Medianus (7 cm above wrist) KCC (flexion of three middle fingers) >KOC (Feels pain distinctly) ACC (slight flexion of two middle fingers) is slightly less than KCC AOC slight or absent (Pain greater at AC than at AO)

M Palmaris Longus No contraction, and he only just feels it

M Supinator Longus KCC (fair) >KOC ACC about the same as KCC AOC is nearly as strong as ACC and stronger than KOC Almost the strongest current yielded by the battery is needed to obtain even KCC

M Biceps KCC (good) >KOC Contractions easily obtained with rheostat 2 to 3 divisions from the maximum The contractions are better than those elicited with the active electrode over the point "N medianus" (7 cm above wrist) immediately after, the current intensity indicated on the milliamperemeter being practically the same

M Extensor Carpi Ulnaris, M Extensor Digiti Minimi, M Extensor Indidis, M Extensor Digitorum Communis Fair contraction, both KCC and ACC, with rheostat three divisions from the maximum (Pain felt rather strongly)

N Medianus (above elbow) KCC Good contraction (flexion of fingers) and considerable pain

The flexion of the fingers is greater than KCC with N medianus (7 cm above the wrist), but there is much less difference between the effects of the galvanic current on the two points than between the effects of the faradic current With the galvanic current pain is quite distinct at both points although stronger at the point above the elbow

Palm of Hand KCC, fair movement of fingers, KCO very slight (Only dull pains at KC) ACO, fair contraction and >ACC

## LEFT ARM FARADIC CURRENT (BROAD ELECTRODE ON BACK)

N Medianus (7 cm above wrist) No contraction and very little sensation with shield one third withdrawn Some contraction with core completely uncovered by withdrawing shield entirely

N Medianus (above elbow) Good contraction (flexion of fingers) with core one-third uncovered and pain Much stronger contraction with shield completely withdrawn than at the lower N medianus point

M Palmaris Longus Fair contraction with shield one third withdrawn The contraction is mainly proximal to the point

M Supinator Longus Fair contraction with shield half withdrawn

M Biceps Good contraction with weakest current (shield not withdrawn at all) He feels it well

M Extensor Carpi Ulnaris, M Extensor Digiti Minimi, M Extensor Indidis, M Extensor Digitorum Communis Contraction with shield one-fourth withdrawn The contraction is mainly proximal to the points stimulated

## RIGHT ARM FARADIC CURRENT (ONE ELECTRODE IN PALM)

N Medianus (7 cm above wrist) No contraction whatever with maximum strength He feels some pain but not much

M Supinator Longus With maximum strength some contraction (dorsiflexion of thumb, index and middle fingers) Pricking sensation mostly in the palm, only a little at position of the other electrode

## LEFT ARM FARADIC CURRENT (ONE ELECTRODE IN PALM)

N Medianus (7 cm above wrist) With maximum strength some contraction of muscles of ball of thumb, etc

M Supinator Longus Fair contraction with maximum strength

M Palmaris Longus No contraction except with maximum strength, which gives fair flexion to fingers

Four blood-flow experiments on as many separate days during a period of three weeks were made on the hands of this patient and one on his feet. The experiments on the feet will be reserved for inclusion in a separate paper on the blood-flow in the feet. A fifth experiment on the hands was partially vitiated for its immediate purpose by the fact that the man came to the laboratory on a rather cold morning with his hands uncovered. This caused a persistently diminished flow in the hands, as is particularly apt to be the case in persons with a habitually poor flow, so that the existence of reflex vasomotor effects from one hand to the other could not be studied under favorable conditions. Nevertheless, the results in this experiment, although quantitatively less marked, were qualitatively the same as in the others.

The question whether in this patient the efferent vasomotor path in the areas where sensation is entirely gone is still capable of conducting vasomotor impulses was studied in the experiments of April 26 and May 2, in which the vasomotor reflexes elicited in one hand by the application of heat or cold to sensitive areas on or near the other hand were determined. The reflex effects on the blood-flow were normal in direction and of considerable intensity.

Thus, in the experiment of April 26 the flow for a period of six minutes before the vasomotor reaction was tested, was 3.90 grams per 100 c c of hand per minute in the right hand, and 4.71 grams in the left. For a fifteen-minute period, immediately preceding the vasomotor test, the flows were, respectively, 3.21 and 4.56 grams. The flow in both hands was slowly increasing up to six or eight minutes before the test. The right hand, it will be remembered, is the weaker of the two, a condition which, in old-standing neuritis, has been found associated with a smaller flow. In neither hand is the flow of normal amount for the age of the patient, and the temperature of the room and calorimeters. This agrees entirely with the fact that his hands were always cold to the touch, although he himself did not know that they were cold. When the right hand was immersed in warm water so deeply that warmth was distinctly felt on the wrist, the flow in the left hand for the first six minutes of the immersion was reduced to 3.56 grams per 100 c c of hand. A rather abrupt increase then occurred, the average flow for a further period of immersion of eight minutes in the warm water being 7.19 grams per 100 c c of hand per minute. The initial diminution of the flow in the hand when the contralateral hand is immersed in warm water is the normal effect, only in this case the diminution is more prolonged than normal. On immersion of the right hand and wrist in cold water, which was well felt on the wrist, the flow in the left was diminished from the average of 7.19 grams per minute to 4.86 grams for the first three minutes and to 2.71 grams for the next twelve minutes, while the right hand continued



in the cold water. The vasoconstriction and vasodilatation in the left hand elicited by thermal stimuli applied to the right hand and appreciated only on the right wrist were therefore perfectly distinct

In the experiment of May 2 the initial flows were 3.03 and 3.08 grams per 100 c.c. per minute for the right and left hands, respectively. When the left hand was immersed in warm water so that the sensation of warmth was only appreciated on the middle phalanx of the left index finger, although there quite intensely, a vasomotor reflex occurred in the contralateral hand with exactly the same features as in the experiment of April 26, viz., a longer initial period than usual, in which the flow was diminished by the application of warmth to the contralateral hand (from 3.03 to 2.67 grams per 100 c.c. per minute for a period of five minutes) succeeded by a very durable increase (to 8.31 grams per 100 c.c. per minute) for the remaining eight minutes, during which the left hand continued in the warm water. The reaction to the immersion of the left hand in cold water was also quite distinct (an eventual reduction of flow in the right hand from 8.31 to 4.29 grams per 100 c.c. per minute)

It is noteworthy, and of course, quite in accord with experimental facts, that a wide-spread and intense vasomotor reflex may be initiated from a very limited receptive area. Therefore, the intensity of the vasomotor reflex in these two experiments is no indication that any portion of the reflex has been elicited from the anesthetic areas of the hands immersed in the warm or cold water. We shall see, however, later on that even the anesthetic areas do contribute something to the total effect, although the contribution is relatively slight.

From these experiments it can be concluded (1) that the efferent vasomotor paths in the parts which are totally anesthetic in this patient are quite capable of conduction, (2) that the centers concerned in reflex vasomotor action on the blood-vessels of a totally anesthetic hand and elicited by heat and cold from areas on or near the anesthetic contralateral hand are quite permeable for vasomotor impulses.

The vasomotor reflex is so good that we can assume that practically the whole efferent vasomotor path to the hand is concerned in it. Therefore, when it is elicited from so limited a receptive surface the relatively small number of fibers in the afferent path must have free access either directly or through the bulbar vasomotor centers to the spinal cells of origin of the afferent fibers for practically the whole of the contralateral hand, not to speak of other areas which very probably are involved in the reaction. This could not well be the case if a lesion existed in the cord, and in the immediate vicinity of the cells of reception of the small afferent path, extensive enough to account for the sensory and motor deficiency in the hands. Assuming, then, that of the three links in the

vasomotor reflex arc, two (the efferent path and the central mechanism) are absolutely or relatively intact, we have now the means of determining the condition of the third link (the peripheral afferent path). This was done in the experiments of May 8 and May 18, in which the behavior of the reflexes in one hand when only the anesthetic parts of the contralateral hand were exposed to heat or cold were studied. It is there shown that the reflexes elicited from the anesthetic areas are feeble in comparison with those elicited from adjacent areas in which sensation is preserved. Thus, in the experiment of May 8 the initial flow in the left hand was 5.25 grams, in the right hand 4.71 grams per 100 c.c. per minute. For the first ten minutes of immersion of the anesthetic portions of the right hand in warm water the flow in the left hand was 4.03 grams per 100 c.c. per minute, which increased to 4.82 grams during continued immersion of the right hand (still only the anesthetic portions) for an additional period of ten minutes. Great care was taken that no part of the hand should be immersed in which the patient preserved any power whatever of temperature sensation. The wrist was carefully protected by cloths from contact with the vessel. When the wrist of the right hand as well as the anesthetic portions of the hand were immersed in warm water so that the patient experienced a distinct sensation of warmth on the wrist, the flow in the left hand, after an initial diminution from 4.82 grams to 4.0 grams per 100 c.c. per minute for a period of four minutes (the normal effect), increased to 6.25 grams during continued immersion of the hand and wrist in the warm water for an additional period of eight minutes. Immersion of the anesthetic part of the right hand in cold water caused the flow in the left hand to diminish to 4.37 grams for the first eight minutes of immersion. The rest of the experiment probably should not be used, as the marked diminution in the flow is a phenomenon often witnessed at the end of long experiments.

In the experiment of May 18 the initial flows were 3.28 and 3.56, respectively, for the right and left hand. Immersion of the right hand (only the anesthetic portions) in cold water caused the flow in the left hand to diminish from 3.56 to 3.19 grams for the first six minutes of immersion. During the next six minutes of immersion of the right hand in cold water the flow increased to 4.42 grams per 100 c.c. per minute, the increase, as is usually the case even in normal hands, beginning abruptly. On immersion of the anesthetic portions of the right hand in warm water a further small increase (to 4.60 grams per 100 c.c. per minute) occurred and this was sustained during the total period of immersion of the right hand in warm water thirteen minutes. Immersion of the anesthetic portions of the right hand in cold water now caused a slight diminution of the flow in the left hand (from 4.6 to 4.38 grams per 100 c.c. per minute for a period of eight minutes). Changes of a very

different order of magnitude were produced when the right hand including the wrist was now immersed in cold water, the flow in the left hand falling from 4.38 to 2.82 grams per 100 c c per minute for the twelve minutes of immersion. The patient felt the cold intensely on the right wrist, not at all on the rest of the hand. Immersion of the right hand and wrist in warm water caused an increase in the flow in the left hand from 2.82 grams to 4.56 grams per 100 c c per minute for a period of five minutes. During the next six minutes, while the right hand and wrist were still immersed in the warm water, the average flow in the left hand sank to 2.89 grams (probably vasoconstriction due to the great duration of the experiment). When the right hand was removed from the warm water, dried carefully and wrapped up in a cloth, the flow in the left hand rose again to 4.26 grams per 100 c c per minute.

#### DISCUSSION AND CONCLUSIONS

From these four experiments taken together the following conclusion seems justified. Since there is no conspicuous defect of conductivity either in the centers or in the efferent vasomotor paths as shown in the first two experiments, and incidentally also in the last two, the defect in the experiments in which only anesthetic areas were exposed to warmth or cold must lie in the afferent portion of the arc, that is to say, in the afferent path from the anesthetic regions through which vasomotor reactions in the contralateral hand can be normally elicited. Further, the lesion as regards the vasomotor path is in all probability a peripheral one involving mainly the afferent fibers and at a level at any rate distal to their cells of reception in the spinal gray matter. The suggestion is that the lesion in the other afferent paths is also peripheral, a question of diagnosis left in doubt by previous clinical examinations. This supports the diagnosis of the case as post-typhoidal neuritis of unusually long duration and with other unusual features.

Perhaps, roughly speaking, we might arrange the various paths as regards the severity of the peripheral lesion as follows: 1. Sensory, including tactile and thermal sensation, pain and also deep sensibility, for example, vibratory. 2. Afferent vasomotor. 3. Voluntary motor. 4. Efferent vasomotor. It is not implied that the whole change is necessarily in the peripheral fibers nor is it perhaps probable, but only that the peripheral fibers are mainly affected. The classification is purely functional. It is not implied, for instance, that Group 2 is anatomically distinct from Group 1. There is, of course, no inherent improbability in the supposition that the efferent and afferent portions of the vasomotor arc are differently affected. The distal neurons of the two paths belong to different anatomical systems, the efferent to the autonomic, the afferent to the cerebrospinal system.

While the changes in the flow in one hand produced by immersing the completely anesthetic portion of the contralateral hand in cold or warm water are not large in comparison with the changes elicited by the application of heat or cold to parts with good temperature sensibility, they seem sufficiently definite to permit the conclusion that even from a part completely anesthetic as regards temperature sensation (as well as regards the other forms of sensation) vasomotor reflexes can be evoked by cold or warmth. Two explanations might be thought of

1 The block which conditions the anesthesia is partially central, *i. e.*, somewhere above the entrance of the afferent fibers into the cord. In this case the afferent sensory paths from the anesthetic areas need not be looked on as totally incapable of conduction of sensory impulses and therefore not incapable of conducting impulses which can cause reflex vasomotor effects

2 The peripheral block being complete for sensory impulses, it is still incomplete for afferent vasomotor impulses. The second condition might depend (a) on the possibility of the reception and conduction by the nerves of skin sensation (particularly in the case we are discussing the nerves which subserve the sensations of warmth and cold) of impulses which can affect reflex vasomotor centers even when they are incapable of receiving and conducting impulses which give rise to the sensations in question, or at least incapable of receiving and conducting them in sufficient intensity to reach threshold value, (b) on the possibility that other afferent fibers than those concerned in sensation exist in the peripheral nerves, through which impulses elicited by heat or cold may pass to vasomotor centers. If such fibers exist there is no reason why they should be involved in exactly the same degrees as the sensory fibers in a chronic peripheral pathological process which is nothing if not selective

That it is not necessary to make the assumption involved in explanation 1 was shown by experiments on a surgical case in which a central lesion could be positively excluded. By an injury to the median nerve in the forearm, certain phalanges were rendered totally anesthetic to warmth, cold and the other forms of cutaneous sensation. A small, but distinct, reflex vasomotor effect on the contralateral hand was obtained on immersion of the anesthetic phalanges in warm or cold water. The subject, a medical student, thoroughly appreciated the object of the experiment, and his statement that during the immersion of the anesthetic phalanges no temperature sensation whatever was experienced, can be taken as strictly accurate. In this case then, the afferent vasomotor path from the anesthetic phalanges was already in some degree permeable when excited by heat or cold at a time when no thermal sensation had returned. As the case had not come under observation at an earlier date it is impossible to say whether the degree of conductivity observed was a

residual phenomenon due to the sparing of the path, or of a portion of it, in the original lesion, or to recovery. It is, of course, conceivable that impulses which can liberate vasomotor reflexes may be capable of being received by, and of passing up, regenerating nerve fibers at a much earlier period than impulses which give rise to sensations. This case is being further studied as regards the return of function by the subject himself under the direction of one of us and will form the basis of a separate paper. The question whether thermal vasomotor reflexes can be elicited from deeper structures than the skin, from muscles, for example, whose afferent fibers when electrically stimulated cause such marked vasomotor effects has an obvious relation to this subject. We have not discussed it because we do not possess the data for doing so. In any case it is certain that the skin, which must bear the brunt of those changes in the external temperature, the adaptation to which is one of the great offices of the vasomotor mechanism, must be far more important in this regard. We have also made no allusion to the possibility that temperature changes, due either to direct conduction or to the passage of the blood from the submerged parts to neighboring parts not involved, or not involved in an equal degree in the lesion, may affect afferent nerves capable of liberating vasomotor reflexes, because if such changes occurred they were too slight or too gradual to elicit sensations of cold or warmth, and it was only with temperature changes which did this that we concerned ourselves.

# VASOMOTOR REFLEXES ELICITED BY HEAT AND COLD FROM AREAS DEPRIVED OF TEMPERATURE SENSIBILITY BY A TRAUMATIC LESION

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In a pathological case already reported in this journal<sup>1</sup> it was shown that vasomotor reflexes, small but definite, could be elicited by the application of heat or cold to areas totally devoid of temperature sensibility. The present communication establishes the same fact, for an otherwise normal subject, in whom anesthesia of certain portions of one hand had been caused by accidental injury to the median nerve in the fore-arm.

## CASE REPORT

*History*—The subject, O C W, is a healthy fourth-year medical student, aged 24. September 15, 1912, at 9 30 a m, he injured his left arm by the breaking of a carboy full of water which he was carrying. The main wound was on the front of the lower part of the forearm. In addition there was a small wound on the dorsal aspect of the little finger. From the way in which the carboy was being held the tendons in the lower part of the forearm and at the wrist were on the stretch and stood out, so that they could easily be severed by a relatively superficial wound. The bleeding, so far as could be observed, was entirely venous and capillary. Certainly no large artery was cut. The hemorrhage was controlled by the patient himself by pressure around the wrist with the right hand until assistance was procured. He was taken to a hospital and under gas anesthesia eight flexor tendons which were found divided were sutured, and in addition the tendon of the extensor digiti quinti proprius on the dorsum of the little finger. A careful search was made in the wound for divided nerves but no large nerve was found. The wound was closed and a splint put on the arm and hand. The arm was dressed morning and evening for the first few days and afterward each day, and healing occurred without complication.

During the interval (4½ hours) between the injury and the operation the patient was able to make the following observations:

*Motor Changes*—Immediately after the accident it was impossible to flex either the thumb or the index finger or any of their phalanges, but adduction and abduction of the thumb and index were not impaired. The middle, ring and little fingers could be flexed, the deep tendons being intact. The hand could not be flexed on the wrist. The little finger could not be extended.

*Sensory Changes*—The entire index finger became numb immediately. This numbness later involved more or less the whole of the hand, but was most marked on the radial side of the palmar aspect.

The patient continued from time to time to make observations.

September 20, 1912. The numbness, except on the index finger, has changed into an intense burning and tingling sensation which involves the thumb, middle finger, radial side of ring finger and the radial half of the palm. The little finger

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\* From the H K Cushing Laboratory of Experimental Medicine, Western Reserve University.

1 Stewart and Laffer. THE ARCHIVES INT MED, 1913, 21, 365. (See preceding paper.)

and the ulnar half of the palm are not involved in this sensation and the same is true of the dorsal, ulnar and palmar surfaces of the ring finger. The skin over the area involved in this sensation as well as that over the index finger is very dry. The furrows of the skin in this region are noticeably white. There is some swelling in the index and middle fingers.

September 30, 1912. The splint was removed to day. The sensation of burning and tingling remains the same and is limited as above described. It is like the pain of a burn exposed to the air and is worse at night. The skin has the same appearance as before and is still very dry. On the palmar surface of the third phalanx of the middle finger a small area about 1 cm in diameter can now be delimited which is very sensitive to light stroking (cotton wool or brush). This hypersensitive spot was first noticed in the latter part of the first week. This area and the rest of the phalanx are anesthetic as regards pain (pin prick), deep pressure, heat and cold. The anesthetic area (to touch, pain, pressure, heat and cold) involves the palmar surface of the thumb, the radial half of the palm, the palmar surface of the index and middle fingers and the entire periphery of the second and third phalanges of the index and middle fingers. The radial side of the ring finger has a certain degree of hypesthesia. The involved area is more or less sensitive to light stroking the middle finger most, the index finger least. On the middle finger especially such stroking is quite painful while hard rubbing causes no pain. A mere touch on the middle finger, especially the palmar surface, caused discomfort, whereas prolonged stroking or (light) rubbing was necessary to produce the same sensation on the index finger. This hypersensitive condition appeared about the second week while the splint was still on. Sensation is normal on the dorsum of the thumb up to and around the nail, also on the dorsum of the first phalanx of the index and middle fingers. The sides of the first phalanx of the index and middle fingers are normal. The skin over the involved area is desquamating. Motion of the whole hand and of the fingers is greatly limited.

October 10, 1912. Motion much improved. Sensation the same as before, but the painful sensations are less intense. The palm and palmar surface of the middle finger are not so sensitive to light contact (stroking). Cannot localize contact. Cannot distinguish pressure at two points. Thermic sensation absent in the entire involved area.

October 20, 1912. Motion better. Can flex all fingers into the palm. Deep flexor tendon to index does not work, does not flex the terminal phalanx. Tactile sensibility is not appreciably improved. Localization and discrimination of the shape, etc., of a body touching the skin are absent.

November 10, 1912. Motion better. Otherwise no change.

December 10, 1912. Skin over the involved area not so dry. Obviously there is now some sweat secretion but still much less than on the normal skin. Occasional shooting pains starting about the wound and shooting to the ends of the index and middle fingers. On tapping lightly over the scar a sensation similar to that caused by a weak electric shock is transmitted to the ends of the index and middle fingers, never transmitted elsewhere.

December 19, 1912. Accidentally burnt the palmar surface of the terminal phalanx of the index finger. The finger was in contact with a radiator and the patient was quite unconscious it was being burnt. A large blister formed in about an hour.

December 20, 1912. The blister was opened and drained by puncturing with a needle through healthy skin at the side. It began to fill immediately and in a few minutes was as large as before. It was reopened and filled again very quickly and this process was repeated about fifteen times during the day.

December 21, 1912. The skin over the blister was cut off and the accumulation of liquid stopped at once. There was no recurrence of the formation of liquid. No pain was felt from the burn at any time. It was so deep as to involve the fat pad. By January 7, 1913, the burn was completely healed.

December 23, 1912 The distribution of sweat secretion and sensation was carefully tested in the laboratory

*Sweat Secretion*—There is no question that the area deficient in sweat secretion is much smaller than at first, or even than a month ago The hand was wrapped in a towel after being wiped dry and put into a hot-air oven The oven contained a dish of water to help to keep the air moist and thus hinder evaporation of the sweat Sweat secretion is still small or absent over an area on the ball of the thumb about  $3\frac{1}{2}$  cm long by 2 cm broad The edge of this area approaches the cleft between the thumb and index finger On the rest of the radial portion of the palm and on the second and third phalanges of the middle finger, where sweating was absent before, it is now present to a certain extent

*Sensation, Radial Half of Palm*—The small area on the ball of the thumb in which sweat secretion is absent is totally insensitive to light touch (with blunt pencil point, cotton wool or brush) To pressure it is sensitive If a blunt point is pressed down with more than a certain amount of force the pressure sensation goes on to definite though delayed pain sensation This area is less sensitive to pressure than the rest of the ball of the thumb With a tube containing water at 3 C no cold sensation on this small area, but with a chip of ice a sensation of cold is obtained though delayed No sensation of warmth with a tube containing water at 45 C, nor was there any effect for some distance outside the boundary Hotter water (50 C) is felt as warm on points just outside although not felt at all inside the boundary, whereas elsewhere on the palm it is felt as hot The rest of the radial half of the palm is sensitive to touch (light contact of blunt point, light stroking with cotton or brush), pressure (with rubber pad of pencil), pain (pin-prick) heat and cold (chip of ice) While ice causes cold sensation everywhere on the palm of the hand it is somewhat less marked on the ball of the thumb and over the radial half of the palm than over the rest of the palm, rather a cool sensation than that of ice

*The thumb* is sensitive to light touch but on the palmar surface of the second phalanx, although a tactile sensation is elicited, the subject cannot tell anything about the kind of body touching him, for example, whether it is pointed or not Pressure sensation is fair on the palmar surface of the thumb and good on the dorsum Ice gives no sensation of cold on the palmar surface of the second phalanx, elsewhere the normal sensation The pin-prick, which elsewhere on the thumb causes pain, elicits only the sensation of contact on the palmar surface of the second phalanx

*The little finger* is normal The more detailed examination of the remaining three fingers follows

*Light Touch—Index Finger, Palmar Surface*—On the second and third phalanges no sensation to simple touch but some sensation to pressure, not going on to pain even with strong pressure with a blunt point On the first phalanx touch is felt but the shape of the object is not discriminated *Dorsal Surface*—Third phalanx only slight sensation of touch without discrimination of nature of object Second phalanx much better touch sensation First phalanx normal *Ulnar Surface*—Third phalanx no tactile sensation Second phalanx fair, third normal *Radial surface*—Third phalanx poor tactile sensation, second pretty good, first normal

*Middle Finger*—Hyperesthetic to light touch on palmar aspect, elsewhere much the same as the index

Light stroking with cotton wool or brush shows much the same distribution of anesthesia over the whole involved area as in the other tests

*Cold—Index, Palmar Surface*—Second and third phalanges no cold sensation to ice First phalanx, little if any cold sensation, perhaps a slight sensation after a long application of the ice *Dorsal and Radial Surfaces*—Second and third phalanges no cold sensation First phalanx normal *Ulnar Surface*—Second and third phalanges, no cold sensation First phalanx, cold sensation but delayed



*Middle Finger, Palmar Surface*—No cold sensation on any of the phalanges, but the contact of ice gave a sensation of touch on all *Dorsal, Radial and Ulnar Surfaces*—Second and third phalanges, no cold sensation, first phalanx normal

*Ring Finger*—Palmar, dorsal and ulnar surfaces normal *Radial Surface*—First and third phalanges normal a small area about 5 mm distal to the joint between the first and second phalanges on the radial side and overlapping the dorsal surface of the second phalanx either gives no cold sensation with ice or the sensation is markedly delayed

The application of a point of ice to the point on the scar in the forearm, mechanical stimulation (tapping) of which gives a sensation like a weak electric shock running down to the index and middle fingers causes no effect except a local sensation of cold over the point touched. On no part of the anesthetic area is anything except a local sensation of cold obtained on contact with ice. No "peripheral reference" of cold<sup>2</sup> could be demonstrated at this stage at any part of the anesthetic area

*Warmth (warm tube)*—*Index Finger, Palmar Surface*—No sensation of warmth on any phalanx. Sensation of contact on first phalanx. *Dorsal Surface*—Warmth felt on first phalanx, nothing on second and third

*Middle Finger*—The same portions are sensitive to warmth as to cold and in about the same degree

*Ring Finger*—Normal except the small area on the second phalanx which was insensitive to ice. This area gives the sensation of warmth with a tube which elsewhere gives a hot sensation

*Pain (pin prick)*—*Index Finger, Palmar Surface*—Only sensation of contact is given on first phalanx except with considerable pressure, when pain is elicited. Second and third phalanges give only sensation of contact to pin prick and heavy pressure is required to elicit even this. No discrimination of the nature of the object. *Dorsal Surface*—First phalanx normal. Second phalanx greater pressure of the pin needed to give pain than on normal skin. Third phalanx no pain, even with considerable pressure, only an indefinite contact sensation

*Middle Finger, Palmar Surface*—All the phalanges are hyperesthetic. A pin-prick gives definite pain, much more intense than on the rest of the skin. Second and third phalanges are more sensitive than the first. Light contact or a light prick gives most pain. Pressing or rubbing hard with a flat surface does not give pain, nor does pinching. Light stroking gives a sensation of exaggerated tickling which is almost pain

*Ring Finger*—Normal to pin prick except the small area which is abnormal to temperature sensation. On this area a pin prick gives sensation of contact and not of pain

*Pressure (with rubber pad of pencil)*—*Index, Palmar Surface*—First phalanx, fair sensation, diminishing on second phalanx toward third phalanx. *Dorsal Surface*—First phalanx normal. On third phalanx pressure sensation is barely obtainable. Second phalanx intermediate

*Middle Finger, Palmar Surface*—Good pressure sensation on all phalanges but accompanied with tingling. *Dorsal Surface*—First phalanx normal. Second phalanx fair sensation, and better than on second phalanx of index finger. Third phalanx about the same as second phalanx of index finger, on increasing the pressure the pressure sensation goes on to pain, which is not the case on the second and third phalanges of the index finger

*Ring Finger*—Normal everywhere

January 21, 1913. Light touch (stroking with brush) is felt over the whole of the involved area but only slightly on the second and third phalanges of the index finger. On the palmar surface of the middle finger the sensation is one of exaggerated tickling. No area can now be found on the ball of the thumb which is insensitive to contact (brush or blunt pencil point). The radial portion of the palm is moist although dryer than the rest of the palm

January 24, 1913 Peripheral reference of cold cannot be obtained Sensation of cold over the scar is delayed

The subject came under observation of the senior author for the first time, a month after receiving the injury The first blood-flow examination was made Oct 15, 1912

October 15, 1912 The blood flow and vasomotor reflexes of the hands were examined after the subject's day's work as a medical student Pulse 112 (sitting) Hands in bath at 4 12 p m Hands in calorimeters at 4 35 p m The hands were kept in the bath for a longer time than usual owing to accidental

TABLE 1—CALORIMETRIC TESTS OF BLOOD-FLOW IN HANDS OF O C W

Time	R	L	Notes	Time	R	L	Notes
4 34	31 02	31 10		4 45	31 42	31 43	Room 22 8 C
4 36	31 02	31 10		4 46	31 46	31 46	
4 37	31 04	31 12		4 47	31.495	31 495	
4 38	31 07	31 15	Room 22 6 C	4 48	31 52	31 52	
4 39	31 10	31 19		4 49	31 535	31 53	
4 40	31 13	31 22	Room 22 6 C	4 50	31 56	31 55	Room 22 9 C
4 41	31 20	31 26		4 51	31 56	31 56	
4 42	31 25	31 31	Room 22 5 C	4 52	31 585	31 57	Room 22 9 C
4 43	31 31	31 34		4 53	31 595	31 585	† *
4 44	31 38	31 39					
Time	R		Notes	Time	R		Notes
4 54	31 595		Room 22 9 C	5 15	32 335		
4 55	31 61			5 16	32 395		
4 56	31 65			5 17	32 45		
4 57	31 69		Room 23 1 C	5 18	32 48		At 5 18 whole left hand into cold water
4 58	31 71						Room 23 4 C
4 59	31 73		Room 23 1 C	5 19	32 495		
5 00	31 785			5 20	32 505		
5 01	31 81		Room 23 0 C	5 21	32 535		Felt the cold water sha:
5 02	31 825		At 5 02 anesthetic phalan-	5 22	32 57		at first but is now get
5 03	31 845		ges immersed in water at	5 23	32 59		used to it
5 04	31 89		43 4 C	5 24	32 60		Room 23 35 C
5 05	31 91			5 25	32 61		
5 06	31 96			5 26	32 625		Hands out of calorimete
5 07	32 01						5 26
5 08	32 08			5 38	32 46		Temp of L is now 31 0
5 09	32 11						Cooling of R 0 165 deg
5 10	32 16		At 5 10 whole left hand put				in 12 minutes
5 11	32 18		into water at 42 6 C				Cooling of L 0 545 deg
5 12	32 22		Room 23 3 C				in 45 minutes
5 13	42,265						
5 14	32 29						

† At 4 53 the anesthetic phalanges of left hand immersed in water at 8 2 C

\* The hands were cautiously immersed so that the subject should not feel the cold water, the hand and wrist being kept from contact with the vessel by a towel On their first introduction into the cold water the anesthetic phalanges were immersed for a moment rather too deeply, so that he felt what he termed a suspicion of cold The fingers were at once withdrawn a little and thereafter he had no sensation of cold whatever

delay in the preparations 3,015 cc of water in each calorimeter Volume of right hand 447 cc, of left 436 cc Rectal temperature 37 15 C Height 5 feet, 7½ inches Weight 146 pounds Came in from street not wearing gloves

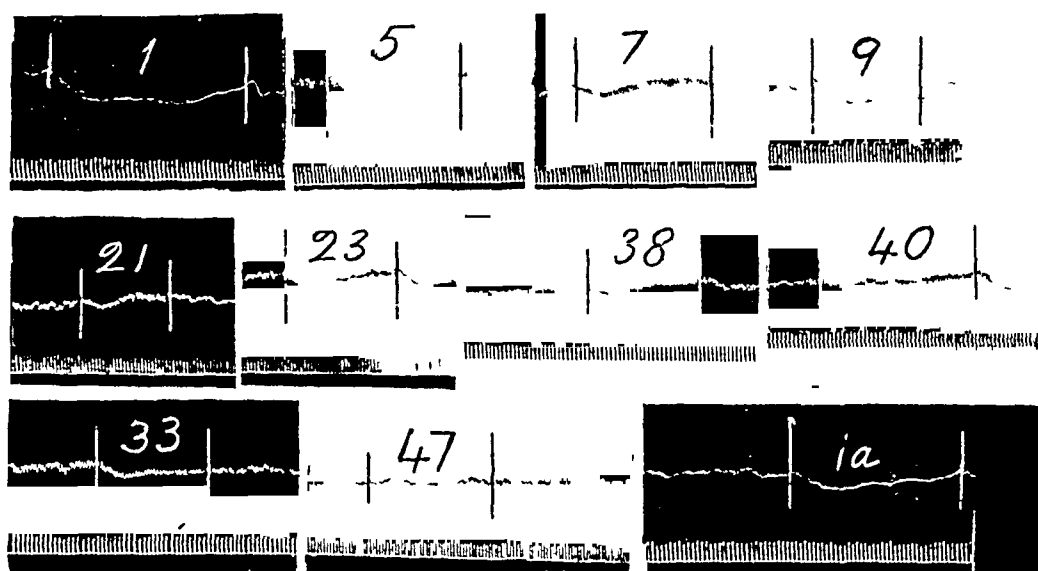
In this experiment immersion of the anesthetic phalanges of the left hand in cold water caused a definite though transient diminution of the flow in the right hand (from 7 39 to 3 82 grams per 100 cc per minute) for the first two minutes of immersion For the next seven minutes

while the anesthetic phalanges continued in the cold water the flow increased to 7.58 grams. For the whole nine minutes the flow was diminished from 7.39 to 6.75 grams per 100 c.c. of hand per minute. The initial flow in the left hand was somewhat less than that in the right (6.83 grams per 100 c.c. per minute). A considerable and more persistent increase in flow followed the immersion of the anesthetic phalanges

TABLE 2—CALORIMETRIC TESTS OF BLOOD FLOW IN HANDS OF O. C. W.

Time	R	L	Notes	Time	R	L	Notes
11	30 93	30 90	Room 23 1 C	2 19	31 265	31 265	Room 23 3 C
13	30 89	30 93		2 20	31 31	31 31	
14	30 93	30 99	Room 23 3 C	2 21	31 36	31 34	Room 23 2 C
15	30 99	31 04		2 22	31 40	31 39	Room 23 3 C
16	31 06	31 10	Room 23 3 C	2 23	31 44	31 41	At 2 23 anes- thetic phalanges put into water at 8 C
17	31 12	31 16					
18	31 195	31 205	Room 23 3 C				
Time	R	Notes	Time	R	Notes		
24	31 46		2 54	32 67			
25	31 48	Room 23 3 C.	2 55	32 705	At 2 55 whole left hand put in water at 8 C		
26	31 515						
27	31 55	Room 23 3 C	2 56	32 74	Room 23 1 C		
28	31 59		2 57	32 775			
29	31 63	Room 23 2 C	2 58	32 795			
30	31 69	Room 23 3 C	2 59	32 825			
31	31 73		3 00	32 85			
32	31 78	Room 23 3 C	3 01	32 875	Room 23 3 C		
33	31 805	At 2 33 anesthetic phalan- ges put into water at	3 02	32 895			
34	31 825	43 5 C	3 03	32 895			
35	31 85		3 04	32 90	At 3 04 dried and wrapped left hand in warm cloth		
36	31 89		3 05	32 91	Room 23 3 C		
37	31 92		3 06	32 925	Room 23 1 C He says the left hand feels warm		
38	31 96	Room 23 4 C	3 07	32 935			
39	31 99		3 08	32 955			
40	32 04		3 09	32 97			
41	32 08	Room 23 4 C	3 10	32 975			
42	32 115		3 11	32 975	Room 23 3 C		
43	32 16	Room 23 3 C	3 12	33 02	Hand removed from calori- meter at 3 12		
44	32 195	At 2 44 whole left hand put in water at 43 C	3 28	32 86	Temp of L is now 30 695 C Cooling of R 0 16 degrees in 16 minutes Cooling of L 0 715 degrees in 65 minutes Vol of right hand 431 cc Vol of left hand 407 cc Rectal temperature 37 05 C		
45	32 32	Room					
46	32 265	23 3 C					
47	32 30						
48	32 355	Room 23 3 C					
49	32 395						
50	32 44	Room 23 3 C					
51	32 51						
52	32 57	Room 23 3 C					
53	32 61						

in the warm water (from 7.58 to 10.58 grams per 100 c.c. of hand per minute for a period of eight minutes). When the whole left hand was now immersed in the warm water some further increase in the flow of the right hand (to 11.14 grams per 100 c.c. per minute for a period of eight minutes) ensued, and this was promptly cut down to 7.24 grams when the whole left hand was immersed in the cold water. Not only was the diminution greater when the whole hand was immersed, but it was



Description of Figure 1—Finger plethysmograph tracings. The tracings are to be read from left to right. The periods of immersion of the parts to which cold or warm water was applied are indicated by the vertical lines drawn through the curves. The signal trace which marked the moment of immersion and withdrawal has been omitted. Time is marked in seconds.

1 Right middle finger of S, a normal man, in plethysmograph. Left hand in cold water ( $8^{\circ}\text{C}$ ) for the period comprised by the vertical lines drawn through the curve. The shrinking of the finger (fall of the curve) is evident.

5 Right middle finger of W in plethysmograph. Whole left hand in cold water ( $8^{\circ}\text{C}$ ).

7 Right middle finger of W in plethysmograph. The anesthetic phalanges of left hand in cold water ( $8^{\circ}\text{C}$ ).

9 Right middle finger of S in plethysmograph. Distal half of left hand in cold water ( $8^{\circ}\text{C}$ ).

21 Right middle finger of W in plethysmograph. Anesthetic phalanges of left hand in warm water ( $45^{\circ}\text{C}$ ).

23 Right middle finger of W in plethysmograph. Second and third phalanges of ring, and third phalanx of little finger of left hand in warm water ( $45^{\circ}\text{C}$ ).

33 Right middle finger of W in plethysmograph. The anesthetic phalanges of left hand in cold water ( $8^{\circ}\text{C}$ ).

38 Right index finger of W in plethysmograph. Anesthetic phalanges of left hand in warm water ( $43^{\circ}\text{C}$ ).

40 Right index finger of W in plethysmograph. Second and third phalanges of ring finger and third phalanx of little finger of left hand in warm water ( $43^{\circ}\text{C}$ ).

47 Second and third phalanges of left index finger of W in plethysmograph. Whole right hand in cold water ( $6.5^{\circ}\text{C}$ ).

1-a Right middle finger of W in plethysmograph. The anesthetic phalanges of left hand in cold water ( $6.9^{\circ}\text{C}$ ). This was the first immersion of the phalanges.



also more persistent than when the anesthetic phalanges alone were exposed to the cold water

After an interval of two months another examination was made

December 19, 1912 Tested thermal sensibility of left hand before the experiment No sensation to immersion in warm or cold water on middle finger, at least up to the upper third of the second phalanx On the index finger no sensa-

TABLE 3—EXPERIMENT 3 WITH RIGHT HAND IN CALORIMETER

December 21, 1912 Right hand put into bath at 11 18 a m Left hand in an Pulse 104 (sitting) At 11 28½ right hand put into calorimeter

Time	R	Notes	Time	R	Notes
11 28	30 60		12 04	32 10	
11 29	30 53	Room 22 7 C	12 05	32 155	
11 30	30 54	Room 22 9 C	12 06	32 20	
11 31	30 57		12 07	32 26	Room 23 C
11 32	30 625	Room 22 9 C	12 08	32 25	
11 33	30 69		12 09	32 32	Room 23 1 C
11 34	30 75	Room 22 9 C	12 10	32 35	
11 35	30 795		12 11	32 39	
11 36	30 855		12 12	32 43	Room 23 1 C At 12 12 the
11 37	30 91		12 13	32 46	7 phalanges put in water
11 38	30 97	Room 22 9 C	12 14	32 48	at 8 2 C
11 39	31 02		12 15	32 51	Room 23 2 C
11 40	31 07	At 11 40 anesthetic phalan- ges put in water at 8 1 C No sensation	12 16	32 535	
11 41	31 095	Room 22 9 C	12 17	32 56	Room 23 35 C
11 42	31 12		12 18	32 585	
11 43	31 165	Room 23 C	12 19	32 605	
11 44	31 205		12 20	32 63	Room 23 3 C
11 45	31 25	Room 22 8 C	12 21	32 655	At 12 21 whole left hand
11 46	31 305		12 22	32 68	put in water at 43 C
11 47	31 365	Room 22 8 C	12 23	32 705	Room 23 4 C
11 48	31 42		12 24	32 74	
11 49	31 49		12 25	32 78	
11 50	31 53	At 11 50 anesthetic phalan- ges put in water at 42 8 C	12 26	32 82	
11 51	31 55		12 27	32 86	Room 23 3 C
11 52	31 59	Room 22 6 C	12 28	32 90	
11 53	31 62		12 29	32 945	Room 23 2 C
11 54	31 675	Room 22 6 C	12 30	33 02	Hand out of calorimeter at
11 55	31 73	Room 22 5 C	12 44	32 86	12 30
11 56	31 77				Cooling of calorimeter R 0 16
11 57	31 81	Room 22 5 C			degrees in 14 minutes
11 58	31 87				Cooling of control calori- meter (without hand)
11 59	31 915				from 30 53 to 29 76 de- grees, or 0 77 degrees in
12 00	31 965	At 12 00, 7 phalanges of left			71 minutes
12 01	31 995	hand put in water at 42 C			Rectal temperature 37 C
12 02	32 02	Room 22 7 C			Vol of right hand 431 cc
12 03	32 06	Room 22 8 C			

tion on immersion at least up to a level well above the second interphalangeal joint A perfectly safe level of immersion was thus determined beforehand An hour before he had burned the flexor surface of the third phalanx of the index finger on a radiator without knowing it and there was a blister on it He washed his hands in warm water before they were put into the bath at 2 p m Pulse 104 (sitting) Hands in calorimeter at 2 12 In testing, the anesthetic phalanges were passed through a hole in a thick plate of cork to avoid contact of sensitive skin with the vessel or water

In the experiment of December 19 the flow for ten minutes before the vasomotor reflex was tested was 10 63 grams per 100 cc per minute for

the right hand and 10.23 grams for the left. For the first two minutes of immersion of the anesthetic phalanges of the left hand in cold water the flow in the right hand sank to 5.21 grams, rising again to 9.15 grams per 100 c.c. per minute for the remaining eight minutes during which the anesthetic phalanges continued in the cold water. On transferring the anesthetic phalanges to warm water the flow in the right hand diminished for the first four minutes to 7.80 grams per 100 c.c. per minute, to increase again to 9.45 grams for the remaining seven minutes of the period of immersion. When the whole left hand was immersed in

TABLE 4—SUMMARY OF BLOOD

Date	Temp. C. of Calorimeter				Vol. of Hands, c.c.		Heat given off (small cal.)		
	Room	R	L	Art. Blood	R	L	R	L	In mins.
Oct. 15	22.6	31.32	31.35	36.65	447	436	2537	2273	16
	22.8	31.61					155		2
	22.9	31.72					1053		7
	23.0	31.87					431		3
	23.1	32.04					1157		5
	32.2	32.23					638		4
	23.2	32.39					915		4
	23.3	32.55					956		8
Dec. 19	23.3	31.17	31.17	36.55	431	407	2219	2018	10
	23.3	31.46					206		2
	23.3	31.64					1394		8
	23.3	31.87					567		4
	23.35	32.06					1153		7
	23.3	32.25					464		3
	23.3	32.50					1669		8
	23.2	32.81					1032		9
Dec. 21	23.25	33.01					1032		8
	22.9	30.82		36.50	431		2012		9
	22.9	31.10					242		2
	22.9	31.33					1684		8
	22.6	31.58					416		3
	22.5	31.79					1448		7
	22.7	31.99					263		2
	22.95	32.23					1782		10
	23.25	32.54					1110		9
	23.35	32.70					440		3
	23.25	32.98					1160		6

the warm water the flow in the right hand for the first three minutes was 9.27 grams, which increased to 13.27 grams per 100 c.c. per minute for the remaining eight minutes of the period. The whole left hand was then put into cold water and the flow in the right sank to 7.90 grams per 100 c.c. per minute during the nine minutes of immersion, to rise again to 9.39 grams (over a period of eight minutes) when the left hand was dried and wrapped up.

In both of the above experiments the two hands were originally in the calorimeters. In order to test the effect of the immersion on the anesthetic phalanges alone, the left hand had to be taken out and dried

Although the drying was carefully done, it might be objected that the effect on the flow in the right hand following the first immersion of the anesthetic phalanges was really due to stimulation of the temperature nerves in the normal portions of the still moist left hand. Of course, this possibility could only apply to the first immersion of the anesthetic phalanges and not to succeeding immersions. Yet it was considered desirable to eliminate it and this was done in the experiment of Dec 21, 1912, in which only the right hand was put into a calorimeter, the left being kept dry until the moment for immersion of the anesthetic phal-

## FLOW OBSERVATIONS ON O C W

Flow in Hands per min		Flow per 100 c c per min		Notes
R	L	R	L	
33 05	29 78	7 39	6 83	Before vasomotor reflex tests
17 08		3 82		Anesthetic phals in cold water (first 2 mins)
33 90		7 58		Anesthetic phals in cold water (next 7 mins)
33 39		7 24		Anesthetic phals in warm water (first 3 mins)
55 77		12 47		Anesthetic phals in warm water (next 5 mins)
40 09		8 96		Whole left hand in warm water (first 4 mins)
59 66		13 34		Whole left hand in warm water (next 4 mins)
32 38		7 24		Whole left hand in cold water
45 82	41 67	10 63	10 23	Before vasomotor reflex tested
22 48		5 21		Anesthetic phals in cold water (first 2 mins)
39 43		9 15		Anesthetic phals in cold water (next 8 mins)
33 65		7 80		Anesthetic phals in warm water (first 4 mins)
40 76		9 45		Anesthetic phals in warm water (next 7 mins)
39 96		9 27		Whole left hand in warm water (first 3 mins)
57 23		13 27		Whole left hand in warm water (next 8 mins)
34 06		7 90		Whole left hand in warm water (first 3 mins)
40 49		9 39		Whole left hand dried and wrapped up
43 73		10 14		Before vasomotor tests
24 89		5 77		Anesthetic phals in cold water (first 2 mins)
45 26		10 50		Anesthetic phals in cold water (next 8 mins)
31 31		7 28		Anesthetic phals in warm water (first 3 mins)
48 79		11 32		Anesthetic phals in warm water (next 7 mins)
32 39		7 51		7 phals left hand in warm water (1st 2 mins)
46 37		10 75		7 phals left hand in warm water (next 10 min)
34 60		8 02		7 phals of left hand in cold water
43 27		10 04		Whole left hand in cold water
61 02		14 15		Whole left hand in warm water (next 6 mins)

anges. As in the previous experiment, a sheet of thick cork with a hole through which the anesthetic phalanges passed prevented any contact of the rest of the hand with the cold or warm water or the container.

It will be seen that the results are precisely the same as in the other experiments. For nine minutes before testing the vasomotor reflex the flow in the right hand comes out 10 14 grams per 100 c c per minute. For the first two minutes of immersion of the anesthetic phalanges of the left hand in cold water, the flow in the right sinks to 5 77 grams, to increase to 10 50 grams per 100 c c per minute for the remaining eight



minutes of immersion. When the anesthetic phalanges were now immersed in warm water (the change from the cold to the warm water was made instantaneously without taking the phalanges out of the cork) the flow diminished for the first three minutes to 7.28 grams, to increase to 11.22 grams per 100 c c per minute for the remaining seven minutes of the period of immersion. Immersion in warm water of seven phalanges (second and third of index, middle and ring, and third of little finger) of the left hand, including the anesthetic phalanges, caused now a diminution of the flow in the right hand for the first two minutes to 7.51 grams per 100 c c per minute. For the remainder of the period during which these phalanges continued in the warm water (ten minutes) the flow rose to 10.75 grams per 100 c c per minute. For nine minutes during the immersion of these phalanges in cold water the flow in the right hand declined to 8.02 grams, a more persistent diminution than was caused by immersion of the anesthetic phalanges alone. When the whole left hand was subsequently put into warm water, an increase ensued in the flow in the right hand to 10.04 grams per 100 c c per minute for the first three minutes and 11.15 grams for the remaining six minutes of immersion, the greatest flow witnessed throughout the observation on this case.

In all three experiments, then, a change is produced in the blood-flow in the right hand when a portion of the left hand, totally insensitive to warmth or cold (as well as to other forms of sensation), is immersed in warm or cold water. Although the effect is smaller and more transient than that produced by immersion of the sensitive portions of the left hand, it is too definite to be attributed to accidental changes in the circulation.

The question has already been raised in discussing a similar reaction elicited from parts totally devoid of temperature sensibility in a pathological case,<sup>1</sup> whether afferent impulses capable of affecting vasomotor centers can be conducted by the nerves of warmth and cold sensation when they are unable to conduct impulses, at least in sufficient intensity, which give rise to temperature sensations, or whether the reactions are elicited through nerves, for example, those supplying the deeper structures, which can be excited by abrupt variations of temperature, although no result is produced in consciousness, and which can act as the afferent link in the vasomotor reflex arc. The possibility also presented itself that the blood in the anesthetic phalanges was sufficiently cooled or heated during the immersion to cause excitation of nerve endings in parts above the level of the anesthesia. In regard to this last possibility it must be remarked that since no sensation of heat or cold was experienced in such neighboring parts, the suggestion is really included in the ques-

tion as already stated. In the hope of throwing some light on this question plethysmographic observations were made with a view of determining the latent period of the contralateral reflex elicited from the anesthetic phalanges. A finger plethysmograph was adjusted on the opposite hand. The moment of immersion of the anesthetic phalanges was written above the plethysmogram by an electromagnetic signal. It was foreseen that unless this latent period should turn out to be markedly lengthened no deductions could be drawn as to whether conduction of heat to or from a deeper layer than usual or convection of heat in the blood to neighboring parts was essential. For we neither know how rapidly heat would be conducted through a finger with the circulation going on, nor how great a change of temperature would be necessary to excite nerves which gave no sign by a sensation of temperature when the threshold had been reached. As a matter of fact, the latent period turned out to be quite small and not measurably greater than when the reaction was elicited from normal skin (Fig 1). The description of the figure sufficiently elucidates the results. It is, however, worthy of special remark that when the second and third phalanges of the index finger of the left hand were enclosed in the plethysmograph no vasomotor reflex could be elicited from the right hand, even when the whole of that hand was immersed in warm or cold water. The meaning of this can only be that the efferent vasomotor fibers going to the index finger or their endings have not yet regenerated to the point at which they can conduct effective impulses. It is entirely in accordance with this that the spontaneous variations in the finger volume not connected with the respiratory movements and with a period covering several respirations which sometimes appear on the trace of the right middle finger, are absent from the trace of the left index finger. If these non-respiratory waves represent more or less rhythmical variations in vasomotor tone they must be absent from a part whose efferent vasomotor fibers are eliminated. We thus arrive at the conclusion that at a time when the efferent vasomotor fibers of a given part have not regenerated, afferent impulses from the same part elicited by heat or cold and producing no effect in consciousness can cause vasomotor reflexes. It must be remembered that the efferent vasomotor fibers in question are autonomic fibers whose cells of origin are in sympathetic ganglia, whereas the afferent fibers are cerebrospinal, their cells of origin being in the posterior root ganglia. In connection with the vasomotor paralysis of the anesthetic phalanges, the extremely rapid and persistent transudation of liquid into the blister on the terminal phalanx of the index finger is a matter of interest. The normal healing of the region, for it was not in the least delayed nor did any complication what-

ever appear, does not tally with the idea that any essential trophic influence had been removed by the injury to the cutaneous nerves.<sup>3</sup>

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3 Additional note—March 19, 1913. Peripheral reference of cold (to the tip of the index finger) has now been observed for the past ten days when a cold object touches a definite part of the scar in the forearm. It is elicited by the point (2 mm in diameter) of a cylinder filled with ice but more intensely with a larger surface. The local response is inferior in intensity to the referred sensation. No peripheral reference of heat is obtained (confirmatory of Trotter and Davies<sup>2</sup>). No peripheral reference of cold as yet from any other part of the skin. The second and third phalanges of the middle and index fingers still give no response to hot or cold cylinders. But prolonged immersion in water at 43 C (as in the blood flow measurements) now causes the slow development of "something like a warm sensation," and in water at 8 C "tingling as if from cold." Light stroking, contact with a blunt point, and pressure are now appreciated over the whole hand. The index finger is now hypersensitive to stroking (except the dorsum of the third phalanx) and appreciates pain on very strong pressure, as on biting the finger. Blood flow observations in the hands show essentially the same features as at the previous examinations.

# A METHOD FOR THE QUANTITATIVE DETERMINATION OF PEPSIN BY USING A COLLOIDAL SUSPENSION OF EGG ALBUMIN

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## INTRODUCTORY NOTE

The experimental work in this paper was done during October, November and December, 1909, and January, 1910. A report of the work was made before the St. Louis Medical Science Club in February, 1910. The work was repeated during the year 1911 and read before the St. Louis Society of Internal Medicine in May, 1911. About this time our attention was called to the work of Hata, which was unknown to us. This work is practically identical with our method except in some points of technic. Hata's paper was published in November, 1909. After reading this paper we decided not to publish our results. As Hata's work has received practically no attention, it seemed important to us that this work should be known. It is a valuable method for the quantitative determination of pepsin. We submit this paper as a confirmation of Hata's work. We think our method of procedure easier and better adapted for clinical work than Hata's.

Many methods have been worked out for the quantitative determination of pepsin. Among these, Hammerschlag's method may be mentioned. It is open to the objection that the method of estimating the amount of undigested albumin is determined by Esbach's method, which is inaccurate. Mett's ingenious method has not proved accurate. This method takes ten to twelve hours to complete the determination. Nierenstein and Schiff's modification of Mett's method takes twenty-four hours for its completion. According to Sahli, Volhard's method is better than Mett's method for showing digestion in gastric contents containing but little pepsin. This method is too complicated for ordinary use.

Grutznher's carmin method is simple but requires the use of a colorimeter. It also has the objection that its solutions are not stable. The Jacoby and Solms method is valuable, but unfortunately requires an impure form of ricin which is not easily obtained. Their ricin solution gradually deteriorates so that gastric contents tested with old solutions show too high a pepsin content. Fuld and Levison's method requires a

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vegetable protein, edestin, which is difficult to prepare or obtain. This solution also deteriorates on standing. The Gross method is simple in its technic and the material, casein, is easily obtained.

Schorer's refractometric method seems valuable but it is not adapted for general use. Illoway's method is simple but takes too long to complete the determination. Several other methods such as Meunier's, Bettman and Schioder's, Spriggs' and Lieberman's have been reported but have not been extensively used.

In studying these different methods to determine which was most applicable to a problem we had in hand, we decided on the Jacoby-Solms method. We were unable to obtain the impure ricin used by them without importing. While waiting for this we studied their method carefully. It occurred to us that the probable explanation of the Jacoby-Solms method was due to a protein in the impure ricin which was made colloidal by their procedure, because their solution becomes opalescent when ready for use. On investigating the Fuld and Levison method, or edestin method, we found their solution to be opalescent and therefore, in all probability, edestin is a colloidal condition. With these facts in mind it occurred to us that the colloidal egg albumin solution of Hardy might be used for a quantitative determination of pepsin by the dilution or limit method.

Hardy has shown that egg albumin diluted with distilled water in the proportion of one part egg albumin to nine parts of water, filtered and heated, becomes opalescent. By dialysis and the use of the electric current on this solution in faintly acid or alkaline reaction, he has proved its colloidal nature. This colloidal egg albumin solution is used by us in our method of determining the quantity of pepsin in gastric contents.

#### METHOD OF MAKING THE COLLOIDAL ALBUMIN SOLUTION

Our method of making this solution is similar to Hardy's. The white of egg is separated from the yolk and is thoroughly beaten, or, better, vigorously shaken in a flask. It is allowed to stand after shaking until the air bubbles disappear. A measured quantity is diluted nine times with water and filtered through ordinary qualitative filter paper. It comes through the filter paper clear and transparent. The solution is acidified slightly by adding two or three drops of an 0.8 per cent solution of hydrochloric acid to 100 cc of the albumin solution. With the albumin of some eggs it is unnecessary to acidify as the albumin becomes opalescent on heating. In other eggs the albumin solution remains clear when heated. This is especially so if the eggs are old. In our method of making the albumin solution we always acidify, as the results are then constant. Hardy does not acidify and, as a result, the solution does not always become opalescent on heating. Hardy's instructions as to the manner of heating are rather indefinite, so that a certain number of failures result even if the albumin solution is acidified. The heating should be done slowly and the temperature should not be raised higher than 60 or 65 C. If the solution is heated too rapidly the albumin solution remains clear and transparent. By heating slowly the solution can be made in

large quantities instead of using small test-tubes as Hardy suggests. We heat the solution in a large test-tube of 100 c c capacity or in an Erlenmeyer flask over a naked flame. Made in this way, we invariably obtain an opalescent solution which has all the colloidal properties of Hardy's solution.

#### METHOD OF MAKING THE COLLOIDAL ALBUMIN SOLUTION READY FOR DIGESTION EXPERIMENTS

To every 100 c c of albumin solution 50 c c of an 0.8 per cent hydrochloric acid are added. When a few cubic centimeters of this acid are first added a precipitate may form which will clear as the remainder of the acid is added. The resulting solution is a clear opalescent solution, but somewhat lighter in color than the original, as it has been diluted one-third with the acid. We may, for convenience, call this a stock solution of albumin.

#### METHOD OF ESTIMATING THE PEPSIN

All the gastric contents are those of students. The gastric contents were removed at 8 a. m., one hour after a Boas-Ewald test breakfast had been given. The gastric contents were filtered and the pepsin tests made at once. The next step is to make four preliminary dilutions of the filtered gastric content.

Tube 1, 2 c c gastric content,	23 c c distilled water make a dilution 1 to 12.5
Tube 2, 2 c c of tube 1	2 c c distilled water make a dilution 1 to 25
Tube 3, 2 c c of tube 1	4 c c distilled water make a dilution 1 to 37.5
Tube 4, 2 c c of tube 1	6 c c distilled water make a dilution 1 to 50

Into four small test tubes 3 c c of the stock colloidal albumin are placed. Into each of these tubes, 1 c c of the preliminary dilution is placed, commencing with the weakest solution first in order to avoid the more rapid action of the stronger solutions as these others are added. The time error is so small by this method that it is ignored, as it only takes a few seconds to mix the solutions in the four tubes. The tubes were shaken to insure thorough mixing, placed in a water-bath registering 38.5 to 40 C and the time of placing them in the water-bath is noted. If the method of diluting is placed in table form it may appear clearer.

#### PRELIMINARY DILUTIONS OF GASTRIC JUICE

- 1 Dilution 1 to 12.5
- 2 Dilution 1 to 25
- 3 Dilution 1 to 37.5
- 4 Dilution 1 to 50

#### FINAL DILUTIONS IN THE COLLOIDAL ALBUMIN SOLUTION

3 c c of acidified albumin solution	1 c c tube 1 makes a dilution 1 to 50
3 c c of acidified albumin solution	1 c c tube 2 makes a dilution 1 to 100
3 c c of acidified albumin solution	1 c c tube 3 makes a dilution 1 to 150
3 c c of acidified albumin solution	1 c c tube 4 makes a dilution 1 to 200

By consulting the accompanying table it is seen that the resulting solutions in the digesting tubes must be 1 to 50, etc. For instance, 1 c c of Tube 1, dilution 1 to 12.5, diluted with 3 c c of stock albumin solution must be 1 to 50, etc. Furthermore, by this method of procedure the percentage of acid in the digesting tubes is 0.2 per cent. For instance, 1 c c of 0.8 per cent HCl in 3 c c of solution makes a 0.2 per cent solution of hydrochloric acid. The amount of acid in the 1 c c of each dilution of the gastric content is ignored, as we have found such small quantities without appreciable influence on the time of digestion.

No	Time required for clearing (minutes)																														Average	Proportion	Average loss	Proportion																														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30																																		
Total	30	70	55	75	66	60	85	80	82	70	70	48	78	95	55	67	77	85	65	65	60	65	50	74	76	66	90	50	48	10	95	60	70	60	63	85	75	57																										
G C																																																																
Dilution																																																																
1/50	24	17	19	13	33	14	21	11	15	12	23	21	12	10	8	19	25	20	13	21	14	17	23	15	14	20	18	20	13	20	14	13	23	22	17	21	14	19	17	3	1	16	2	1																				
1/100	45	22	29	29	40	26	31	17	28	30	22	35	19	15	13	30	38	27	22	29	25	33	40	23	23	25	30	40	19	47	36	30	39	16	24	38	20	48	12	9	16	7	16	9																				
1/150	60	27	42	32	63	31	42	21	45	40	24	47	30	25	37	42	50	41	34	41	36	40	60	34	31	23	36	75	38	60	55	48	55	26	47	63	37	65	42	2	43	3	7	2	38																			
1/200	70	32	47	41	80	35	50	24	52	50	45	60	35	22	37	55	65	53	50	54	57	55	75	45	47	45	57	90	65	75	65	10	65	32	65	77	51	70	53	5	3	08	42	7	30																			

TABLE SHOWING TOTAL ACIDITY, DILUTION AND TIME REQUIRED FOR CLEARING IN THE DIGESTION OF A COLLOIDAL SUSPENSION OF EGG ALBUMIN

After the tubes have been placed in the water bath, the tube with dilution 1 to 50 is removed at short intervals and examined to determine whether digestion is complete in that tube. Each tube is taken in the order of its dilution and the time of its digestion noted. The end-point of the digestion is when the opalescence has disappeared and the solutions are practically clear. There is always a faint, cloudy appearance after the opalescence disappears. At first this end-point may seem uncertain, but after a few trials one determines this easily. In examining the tubes they must not be placed in direct sunlight or strong light. We read all our tubes at the north window of the laboratory where there is a clear, diffused, reflected light.

The results in this table are consecutive tests made on thirty-eight gastric contents of students. These are considered normal gastric contents as none of them differ much from the so-called normal standard of quantity of gastric contents and total acidity of a Boas-Ewald test breakfast.

It is seen that on the whole, the results are as uniform as we could expect. There is some variation in the time of digestion but not more than in the total acidity. The time of digestion is not proportional to the dilution as the more dilute solutions of the gastric contents digest relatively quicker than the more concentrated.

If we consider the time it takes a dilution of 1 to 50 to digest as one, we find the ratio 1,-1 67,-2 4,-3 instead of 1,-2,-3,-4, the ratio by dilution. The column of averages, No 1, is made by averaging the time digesting all the 38 gastric contents. Column No 2 is made by averaging all except 1, 5, 23, 28 and 36, which digested so much slower than the others as to be somewhat out of proportion to the others. The ratio here is 1,-1 68, 2 4,-2 98, which is practically the same as that of all the contents.

By this method of procedure, supposedly normal gastric contents in a dilution of 1 to 100 will clear colloidal egg albumin approximately in one-half hour. In gastric analysis we consider a normal total acidity between 40 and 70. In a determination of pepsin by this method we might consider the pepsin as normal when digestion is finished in a dilution of 1 to 100 in twenty-five to thirty-five minutes. If in this dilution, digestion is completed more rapidly than thirty minutes, we know there is plenty of pepsin. The only question is how far above thirty minutes we may make the limit and still be within so-called normal limits. It seems to us that a digestion in twenty-five to thirty-five minutes should still be considered normal, as the general average for this dilution is twenty-nine minutes.

In another set of experiments on the gastric contents of thirty-four different students, by a different method of diluting, we obtained the following general average



Dilution	Average, Minutes	Dilution	Average, Minutes
1-8	6 0	1-122	38 0
1-20	9 5	1-140	44 0
1-40	14 0	1-160	50 5
1-80	23 5	1 200	57 0
1-100	30 0		

We see here the general averages approach those of the other set of experiments

Instead of using the time of digesting as a standard we might establish an arbitrary standard. If we consider the digesting power of a dilution of 1 to 100 in thirty minutes as 100, we would have a standard for comparison. If a pure gastric content digested the solution in a dilution of 1 to 100 in forty minutes, the pepsin power would be less as the time of digestion was longer. In units this would be 67, as the digestion was 33 per cent slower. Or if the digestion in the dilution was completed in twenty minutes, the pepsin units would be 133, etc. The normal limits would vary between 85-116, we take the limit as varying between twenty-five and thirty-five minutes.

In the routine examination of gastric contents for the quantitative determination of pepsin, all that is necessary at first would be the making a dilution of 1 to 100 and note the time of the digestion. If this took place between twenty-five and thirty-five minutes we could consider the digestion normal. If it took much longer or did not clear up at all, stronger solution should be used. Let us say a dilution of 1 to 10, 1 to 25. If these cleared in twenty-five to thirty-five minutes the digestion power in units would be 1/10, 1/25 of 100. Any other dilution that the worker might desire to use could easily be made. Dilutions might be made as follows

3 c.c. acidified albumin 1 c.c. filtered gastric content makes dilution 1-4  
 3 c.c. acidified albumin 1 c.c. of 1 to 25 dilution makes dilution 1-10  
 3 c.c. acidified albumin 1 c.c. of 1 to 625 dilution makes dilution 1-25

In making up small quantities of the albumin solution for use at different times, it occurred to us that the albumin of different eggs might vary in concentration and thus the time of digestion might also vary, when the solution of different eggs was used. We tried a 2 per cent solution of pepsin on different eggs and found no marked variations. We also tried a gastric content in different dilutions on two dozen different eggs and found the results practically constant.

There is another question which is of importance, that is, whether the acidified albumin solution is stable. These solutions will keep about ten days or two weeks, but at the end of that time the albumin begins to precipitate and, as a result, the time of digestion is shortened. We also found that the end-point in the old solutions is not so sharp as in the fresh solutions.

The acidified albumin solution with chloroform added in the proportion of one part chloroform to 1,000 albumin solution, keeps from two to three weeks. At the end of three weeks there may be no precipitate of albumin, yet the end-point is not sharp and the resulting time of digestion is somewhat inaccurate.

The time of digestion is not proportional to the quantity of pepsin as measured by the dilution. As the solution of gastric contents becomes more dilute the time of digestion gradually lessens. This suggests the possibility that in the dilution methods such as we have used, we do not obtain the same result we would obtain if the digestion were carried on in undiluted gastric contents. By diluting we may lessen certain inhibitory factors which operate in concentrated gastric contents but not in dilute solutions. However, the results obtained by this method approximate closely the digestive power of a given gastric content. Any marked pathological change in the digestive power of a given gastric content will surely be found by this method, as we have shown conclusively in pathologic cases.

The concentration of hydrochloric acid for the most rapid digestion with this albumin solution is 0.1 per cent. The time of digestion is proportional to the concentration of the albumin used.

The points in favor of this method are

- 1 We have a material which is easily obtained
- 2 The colloidal albumin solution is easily made
- 3 The technic is as simple as any dilution method can be
- 4 The time of making a complete determination is under one hour
- 5 The results are constant

Objections to this method

- 1 The solution cannot be kept and used indefinitely, as it decomposes
- 2 It has the objection, that dilution methods do not give the actual digestion as found in concentrated gastric contents

3 The end-point may seem indefinite to those who use this method for the first time, but experience soon enables one to read and obtain constant results.

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# HEART SIZE AND HEART FUNCTION IN CHILDREN SHOWING ORTHOSTATIC ALBUMINURIA. AN ORTHODIAGRAPHIC STUDY<sup>1</sup>

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The close relationship of orthostatic albuminuria to the cardiovascular system has frequently been emphasized, yet in a consideration of the literature one is struck by the diversity of opinions and the contrary findings of various authors. Having at our disposal the material of a large pediatric clinic and noting how frequently cases of orthostatic albuminuria presented themselves for treatment, we determined to study the hearts and blood-pressures in a number of these patients in order to see which of the previous findings we could corroborate, and also whether in the course of our work we could throw some light on the pathogenesis of these symptoms.

The present paper will deal only with our results in the examination of the heart, and we leave a consideration of the blood-pressures to a future communication.

Ever since Edel<sup>1</sup> called attention to the cardiovascular factor as an important one in the etiology of orthostatic albuminuria, many observations have been made, both on the heart and the vessels, in an attempt to clear up this obscure subject. Although various investigations have not as yet been able to solve the problem, nevertheless in their course a considerable amount of interesting data has been brought forward. At first there was a tendency to explain the albuminuria purely as the result of a cardiovascular abnormality, but it soon became clear that urine of a similar character was excreted by children in whom no physical abnormalities could be detected. On the other hand, it had been noted that a large number of children who showed this urinary anomaly also presented cardiovascular peculiarities. These symptoms appeared to be more or less characteristic, and led Langstein<sup>2</sup> to classify his cases of orthostatic albuminuria in three groups: 1. Children who have grown rapidly, who complain of fatigue, palpitation and headache, look pale, but whose hemoglobin is normal. This type usually occurring in girls of 12 to 14 years, Langstein terms the angiospastic type. 2. Children

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\* From the Dispensing and X-Ray Departments of Mt. Sinai Hospital.

1. Edel. *München med. Wchnschr.*, 1901, Nos. 46 and 47.

2. Langstein. *Die Albuminurien alterer Kinder*, Monograph, Leipzig, 1907.

who flush easily, who show marked vascular irritability, whose complaints are chiefly congestive headaches, vomiting attacks and urticaria. These cases he groups as the *erethic type*. 3 Children whose physical examination shows no abnormality and who have no complaints. In such cases the albuminuria is incidentally found in a routine examination.

It appears, therefore, both from previous observations and from the cases we are about to describe, that when subjective symptoms do occur in orthostatic albuminuria they are chiefly those referable to the cardiovascular system, viz. dyspnea on exertion, palpitation, precordial pain, headache, fainting, hypersusceptibility to cold. These symptoms, coming on as a rule in children between the ages of 10 and 14, have become intimately associated with the symptomatology of puberty. This connection has long been noted, and has led to numerous hypotheses in which a disproportion between the growth of the various organs and the work they are called on to perform at this period of rapid bodily development has been assumed as the basis of these symptoms. An analogy is seen between the albuminuria, which is supposedly due to an insufficiency of the kidney, unable in its growth to keep pace with the rest of the body, and the cardiac symptoms which are an expression of a similar developmental backwardness of the heart.

The material on which this report is based comprises thirty-six dispensary cases, who during the previous fourteen months applied for treatment for a variety of complaints. These complaints, coupled with the more or less characteristic appearance of the children, led us to suspect albuminuria. In each case albumin was shown to be present in the urine by the addition of dilute acetic acid and the application of heat. The albuminuria was then proved to be of the orthostatic variety by the examination of several specimens of the early morning urine, which was found to be albumin free. In a few of the cases albumin only appeared in the urine after the child was placed in the lordotic position by kneeling as described by Jehle<sup>3</sup>. In all the cases the albumin disappeared on the assumption of the horizontal position. In none of the cases were casts found, though centrifuged specimens of the urine were frequently examined, some of them over a period of a year. These cases were subjected to a functional heart examination in the following manner:

A complete physical examination of each child was made in such a manner that the element of fear or nervousness on the part of the child could be excluded as much as possible. Then on another day the heart size was determined by orthodiagraphy in the sitting posture and the pulse-rate taken. The child was next made to run up and down four flights of stairs rapidly and was then immediately orthodiographed a second time and the pulse again counted. The fluoroscopic examination was always done at the same time of the day, sufficiently removed from meal-time to obviate sources of error. The orthodiagraph was in every case made by the same one of us and the physical examination by the other so that the personal element might be eliminated.

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3 Jehle. *Die Lordotische Albuminurie*, Leipzig, and Wien, 1909.

## EXAMINATION OF THE HEART AT REST

In Table 1 will be found the results of the orthodiagraphic examination of these thirty-six children while at rest. In the fifth column are given the average figures of heart size for children of corresponding heights as determined by Veith<sup>4</sup>. A comparison of these figures shows seven of the hearts to be larger than normal. Of these seven cases, six show an increase over the normal of but 1 to 3 mm, differences within the limits of error. This leaves one case (Case 18) in which the heart is distinctly enlarged. Of the remaining twenty-nine cases, twenty-two show values lower than the normal. It is remarkable that the majority of these figures differ from the normal by relatively large amounts—from 1 to 4 cm. In this chart we have included all our cases of orthostatic albuminuria irrespective of the presence or absence of cardiac symptoms. Included in these, however, are fifteen children who either complained of subjective symptoms or presented signs of cardiac abnormality on physical examination. It is, therefore, of interest to determine whether these fifteen can be differentiated from the others in respect to heart size. This is of especial importance in view of the effort which has been made by investigators for some years to find in an alteration in heart size and function an explanation of these very symptoms.

French and German clinicians have advanced various theories to explain these symptoms.<sup>5</sup> As has been mentioned above, it appeared to most observers that since many of these cases occurred at or immediately before puberty, owing to a lack of correspondence of growth between the heart and the body, a relative insufficiency of the former became manifest, accentuated by the excessive psychical and physical demands of the growing body. This weakness showed itself, especially in children, who by heredity or environment, were handicapped by poor physical development. The ensuing malnutrition also expressed itself in poorly developed hearts, with the results that the demands of even every-day life were the cause of subjective and objective signs of heart insufficiency, such as in normal individuals would be manifest only after considerable exertion. To quote Martius<sup>6</sup>: "Heart weakness without expressly discoverable cause, brought about by the ordinary demands of life, incidental to the school age." The same idea has been aptly expressed by Fairbanks,<sup>7</sup> who, in speaking of the "Essential Insufficiency of the Heart in Childhood," says: "One reason why the aggregate of demands on the heart may sometimes exceed its power to respond lies in the fact that the general bodily development is neither synchronous nor symmetrical."

4 Veith *Pädiat. f. Kinderh.*, 1908, lxxiii, 205

5 Lommel *Krankheiten des Junglingsalters*, *Ergeb. d. inn. Med. u. Kinderh.*, 1910, vi

6 Martius *Kongress f. inn. Med.*, 1899, p. 41

7 Fairbanks *Jour. Am. Med. Assn.*, 1907, xlix, 1976

This clinical picture, to which Germain Sée<sup>8</sup> first called attention in 1889, and to which he gave the name "*Hypertrophie et dilatation de la croissance*," was further developed and more completely described by Martius.<sup>9</sup> In the examination of a large number of institution children this observer was impressed by the existence of a distinct group presenting the following typical appearance

The children are weak, pale, lose their appetite, complain of headache. Examination reveals besides slight enlargement of the cervical nodes, moderate anemia, sometimes but not always orthostatic albuminuria, the absolutely characteristic heart finding dilatative weakness.

According to Martius, in this condition the physical signs are characteristic. The apex-beat of the heart is displaced beyond the nipple, sometimes out as far as the anterior axillary line, it is heaving in character, the pulse shows distinct diminution in tension and has a tendency after exercise to increase in rate out of all proportion to the amount of the exertion and at the same time to become very poor in quality. This condition Martius considers frequent among the poorer classes.

While during the past decade orthostatic albuminuria was arousing considerable interest<sup>10</sup> and the children suffering from it were subjected to careful study, it became apparent that a great number of them belonged to the above group described by Martius, the albuminurics showing cardiac signs and symptoms identical with those classed as dilatative weakness. Thus in ninety cases of orthostatic albuminuria Lommel<sup>11</sup> found thirty-eight with cardiac abnormalities, thirteen with apparent left ventricle hypertrophy, eleven with markedly exaggerated apex-beat and nine with systolic murmurs. Schaps<sup>12</sup> in the same way notes a big percentage of enlarged hearts with subjective symptoms. The idea was, therefore, generally accepted that many orthostatic albuminurics had cardiac enlargement. It must be remembered, however, that these observations were made before the introduction of the more precise methods of examination afforded by the x-rays, and it is therefore of considerable interest to find that when a few similar cases were subjected to fluoroscopic examination no enlargement of the heart was found. Fischl<sup>13</sup> who skiagraphed these hearts found them normal, while Langstein and Reyher,<sup>2</sup> using the orthodiagraph, found to their surprise that in eight cases so examined the hearts were smaller than usual. This

8 Germain Sée *Traite des maladies du coeur* 1889

9 Martius *Loc cit* Note 6, and *Gedenkschrift für von Leuthold*, 1906

10 For a review of the latest literature on this subject see Bass *A Summary of the Recent Literature on Orthostatic Albuminuria* *Am Jour Dis Child*, 1912, iv, 246

11 Lommel *Arch f klin Med*, 1903, No 78, p 540

12 Schaps *Arch f Kinderh*, 1903, No 35

13 Fischl *Arch f Kinderh*, 1909, lii

TABLE 1 —HEART SIZE DURING REST IN THIRTY-SIX CASES OF ORTHOSTATIC ALBUMINURIA,  
TWENTY-SIX GIRLS AND TEN BOYS\*

Case No	Age	Height, cm	Heart Size, Transverse Diameter, cm	Normal Heart Size (Veith), cm	Difference, cm	Symptoms and Physical Signs
1		9	115	82	88	— 6 Palpitation, dyspnea
2		10	129	86	94	— 8 Palpitation, dyspnea
3		11	130	84	94	—10 Palpitation, dyspnea, booming first sound
4		8	132	87	987	—11 Palpitation, dyspnea, booming first sound, <i>pulmonic second accentuated</i>
5		14	136	82	987	—16 Palpitation, dyspnea, first sound impure, <i>pulmonic second accentuated</i>
6		14	140	94	987	— 4 Palpitation, dyspnea, booming first sound
7		13	151	91	113	—22 Palpitation, dyspnea, overaction
8		10	131	91	987	— 7 Palpitation, dyspnea, apex one finger out- side nipple, overaction
9		10½	126	96	94	+ 2 Palpitation, dyspnea, left border one finger outside nipple
10		8	121	82	94	—12 Palpitation, dyspnea, apical systolic mur- mur, <i>pulmonic second accentuated</i>
11		11	133	87	987	—11 Palpitation, dyspnea, apical systolic mur- mur
12		12	137	78	987	—2 Palpitation, dyspnea, apical systolic mur- mur, overaction
13		7	115	91	88	+ 3 Palpitation, dyspnea, heaving apical im- pulse, booming first sound
14		14	150	10	1039	— 3 Palpitation, dyspnea, apex outside nipple, heaving impulse, overaction, <i>accentuated pulmonic second</i>
15		12	140	93	987	— 6 Apex, one finger outside nipple, marked tachycardia
16		10½	126	95	94	+ 1 No symptoms or signs
17		12	131	101	987	+ 2 No symptoms or signs
18		11	130	109	94	+15 No symptoms or signs
19		13	141	10	1039	— 39 No symptoms or signs
20		13	157	84	125	—41 No symptoms or signs
21		10	121	102	94	— 8 No symptoms or signs
22		12	128	86	94	— 8 No symptoms or signs
23		9½	121	95	94	+ 1 No symptoms or signs
24		12	126	94	94	0 No symptoms or signs
25		9	117	84	882	— 4 No symptoms or signs
26		12	142	107	1039	+ 3 No symptoms or signs
27		8	112	87	882	— 1 No symptoms or signs
28		11	152	105	113	— 8 No symptoms or signs
29		10	132	85	987	—13 No symptoms or signs
30		15	145	89	1039	—14 No symptoms or signs
31		11	135	87	98	—11 No symptoms or signs
32		14	155	88	125	—38 No symptoms or signs
33		10	132	91	987	— 7 No symptoms or signs
34		12	140	88	987	—10 No symptoms or signs
35		5½	94	77	84	— 7 No symptoms or signs
36		13	130	86	94	— 8 No symptoms or signs

\*The first fifteen cases in this table are those in which symptoms or physical signs of cardiac abnormality were present. The remainder were free from such signs.



discrepancy, though in so small a number of cases, is important enough to deserve further investigation

Returning once more to our own cases, we have placed the children who show either subjective or objective signs of cardiac involvement together at the commencement of Table 1 (Cases 1 to 15) In the last column are enumerated the corresponding signs and symptoms

A study of these fifteen cases shows that in none of them is the heart increased in size Two of them reveal an increase over the normal of 2 and 3 mm, respectively, values which, as was mentioned above, are within the limits of error On the other hand, nine of the remaining show a distinctly small heart, differing in one case by as much as 22 mm from the normal size The hearts are enlarged neither to percussion nor to fluoroscopy, with four exceptions (Cases 8, 9, 14 and 15), in which percussion showed slight enlargement to the left, which was verified, however, by the orthodiagraph only in one instance The significance of the enlargement in this case (Case 9) will be discussed later Our results are, therefore, in accord with the observations of Langstein, Reyher and Fischl, who found no enlargement

In spite of the absence of any demonstrable increase in the size of the hearts, all of these children nevertheless had definite symptoms They commonly complained of dyspnea on exertion, of palpitation, or more rarely, of precordial pain Twelve of the fifteen had definite signs of abnormal function, five had booming first sound, three had apical systolic murmurs, four had marked accentuation of the second pulmonary sound, four showed apical signs of marked over-action and four showed increase of heart dulness to the left These are all distinct signs and symptoms of relative heart insufficiency, and undoubtedly correspond to the cases described by Martius and others as dilatative weakness

It may not be amiss at this point to present in detail the history and physical examination of one of our cases

*History*—R P (Case 8), female of Russian parentage, aged 10 years

*Family History*—An older sister has rheumatic endocarditis for which she has been in the hospital on several occasions Parents well No history of tuberculosis

*Past History*—Measles in early childhood Except for several mild attacks of tonsillitis the child has been well Has never had scarlet fever

*Present Illness*—For the past ten months the patient has noted epigastric oppression, severe dyspnea and palpitation on exertion No cough No sweats No edema No fever Does not vomit Appetite fair Bowels regular Sleeps well

*Physical Examination*—A very nervous child, showing poor muscular tonus, as evidence of which there is a marked exaggeration of the lumbar lordosis Marked pallor of the skin, but lips and mucous membranes strikingly ruddy Hands cold and cyanotic Marked dermatographia Chvostek's sign positive<sup>14</sup>

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<sup>14</sup> For the value of this sign see Bass, "Chvostek's Sign and Its Significance in Older Children," *Am Jour Med Sc*, July, 1912

Mouth, throat, lymph-nodes, eyes negative Chest long and flat, scapulae winged epigastric angle narrow Lungs negative Heart Apex in the fifth space in the nipple line, distinct over-action, percussion shows the left border one finger outside the nipple line, first sound at apex booming in character, no murmurs, second sounds at base accentuated, action regular, somewhat rapid, short venous hum over the vessels of the neck, pulses regular, no increased tension Abdomen lax, right kidney palpable

Orthodiagraphy reveals a heart normal in shape, size and position

Urine A M specimen albumin-free, p m specimen, faint trace of albumin, after lordosis (kneeling for three minutes), very heavy precipitate of albumin

This case, then, presents the typical picture we have above described—a child who comes to us complaining of severe palpitation and dyspnea on exertion, who is suffering from orthostatic albuminuria, whose physical examination by the ordinary methods would lead one to suspect cardiac enlargement However, in spite of the signs of cardiac over-action and the fact that percussion shows the heart dullness one finger to the left of the nipple, careful measurement with the orthodiagraph proves that the heart is normal in size and position

It may be concluded from our findings that the conception "dilatative weakness" as applied to cases of orthostatic albuminuria, at least in so far as it assumes enlargement of the heart, is a mistaken one, due probably to errors in percussion, which will be discussed later on Nor can the small hearts stand in a causative relation to these symptoms, since the smallest heart sizes were found among those children who did not present any symptoms at all

#### EXAMINATION OF HEART SIZE AFTER EXERTION

Having definitely decided that these hearts during rest were normal or under-sized, the next question to be determined was what alteration in size, if any, the heart underwent after exercise

The change in size in the normal heart after exertion has been thoroughly studied by numerous observers since the introduction of precise methods for the determination of heart size Moritz,<sup>15</sup> Dietlen,<sup>16</sup> Kienbock,<sup>17</sup> Agostini,<sup>18</sup> Jundell and Sjogren<sup>19</sup> and many others showed that contrary to the previously current opinions, the normal heart, even after exhausting exercises, contracts considerably in volume It follows from their work that acute dilatation of the healthy heart does not occur Martius, quoted by Langstein,<sup>2</sup> however, believes that cases of dilatative weakness previously referred to react to exertion by an increase in heart size, and therefore concludes that these hearts are weak According

15 Moritz *Munchen med Wehnschr*, 1907, No 14, also 1908, No 25

16 Dietlen *Ergeb der Physiologie*, 1910, also *Munchen med Wehnschr*, 1907, No 10

17 Kienbock, Selig and Beck *Munchen med Wehnschr*, 1907, No 29

18 Agostini *Ztschr f exper Pharm u Therap*, 1909, p 159

19 Jundell and Sjogren Reviewed in *Centralbl f inn Med*, 1912, No 42, p 1053

to Maitius, this symptom is one of the most frequent in orthostatic albuminuria

Schaps,<sup>12</sup> relying on percussion, in an examination of sixteen cases of orthostatic albuminuria showing cardiovascular symptoms or signs, found only one case in which after exercise the heart seemed to have enlarged. This is of particular interest, in view of the fact that of the thirty-five cases described by him, twenty showed pathological heart findings (murmurs, arrhythmia, accentuation of the basic sounds, instability of the pulse)

Neumann<sup>20</sup> in eight cases of dilatative weakness, two of which had albuminuria, found by percussion that after stair-climbing the hearts increased in size

TABLE 2—SHOWING HEART SIZE BEFORE AND AFTER EXERCISE IN CASES OF ORTHOSTATIC ALBUMINURIA\*

Case	Transverse Diameter Before Exercise, cm	Same after Exercise, cm	Difference, cm	Case	Transverse Diameter Before Exercise, cm	Same after Exercise, cm	Difference cm
1	82	79	— 3	19	10	93	— 7
2	86	83	— 3	20	84	84	— 0
3	84	82	— 2	21	102	97	— 5
4	87	83	— 4	22	86	82	— 4
5	82	83	+ 1	23	95	94	— 1
6	94	88	— 6	24	94	93	— 1
7	91	91	— 0	25	84	79	— 5
8	91	91	— 0	26	107	104	— 3
9	96	96	— 0	27	87	8	— 7
10	82	81	— 1	28	105	99	— 6
11	87	86	— 1	29	85	84	— 1
12	78	78	— 0	30	89	86	— 3
13	91	89	— 2	31	87	87	— 0
14	10	92	— 8	32	88	84	— 4
15	93	91	— 2	33	91	88	— 3
16	95	93	— 2	34	88	81	— 7
17	101	97	— 4	35	77	76	— 1
18	109	104	— 5	36	86	?	?

\*This chart shows the heart size before and after exercise. As in chart one the first fifteen cases are those with cardiovascular symptoms or signs

The work of these observers is, however, not beyond criticism, since they relied for the determination of heart size on percussion only. We have been unable to find records of any orthodiagraphic heart examinations before and after exercise, either in cases of orthostatic albuminuria or in cases of dilatative weakness, and consider such an examination absolutely necessary for a conclusive determination of the question of dilatation after exercise. Such examination we have carried out. The exercise consisted in rapidly running up and down 160 steps, which

always resulted in considerable fatigue. The children were then immediately examined on the fluoroscope and orthodiagraphic tracings made under exactly the same conditions and position in which the tracings had been made before exercise.

Table 2 shows in parallel columns the transverse heart diameters in our thirty-six cases before and after exercise. It will be seen that in twenty-two cases the heart became distinctly smaller, while in the rest of the cases it remained unchanged or practically so. In no case did the heart become larger after exercise, not even in the children showing subjective or objective cardiac symptoms. These results definitely prove that the cardiac symptoms in this undoubtedly clinically distinctive group must find an explanation elsewhere than in the altered heart size, possibly in some disturbance in the vasomotor system.

It is noteworthy that although none of the hearts increased in size, thirteen of them failed to grow smaller.<sup>21</sup> (We have included those which diminished only 1 mm, as this was practically no change in heart size.) The failure of these hearts to contract after exercise is the more remarkable and is indicative of some abnormality of heart action, in view of the experience of Moritz that the hearts of youthful individuals and of those who are not accustomed to hard work, show the greatest amount of contraction. The exact significance of this fact we are not in a position to state, it may be looked on as an evidence of abnormal cardiac response, as healthy hearts quite regularly show a distinct diminution in size after exercise.

Various explanations have been advanced to account for the discrepancy between the increased size of the heart as shown by percussion and the actual findings as shown by the more objective methods. Herz,<sup>22</sup> Romberg,<sup>23</sup> Hoffman<sup>24</sup> and other authors have cautioned against the fallacy into which one is easily led, especially in cases of overacting hearts where the force and transmission of the apical impulse to the left, or as some describe it, its "irradiation," give the impression of cardiac enlargement. One is more prone to make such an error in cases with narrow, flat chests in which the heart has perhaps assumed a position absolutely nearer to the axilla because of lessened capacity of the thorax, and in which for the same reason the apex-beat has acquired a more lateral position in relation to the nipple. In addition, on exertion, with its resultant dyspnea, a transitory emphysema is produced whereby the diaphragm is pressed downward, pulling with it the apex of

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21 In the estimation of heart size we have utilized the transverse diameter of the heart rather than the superficial heart area, as recommended by Moritz and Dietlen, owing to the errors inherent in the latter method.

22 Herz *Med Klin*, 1903, p 778

23 Romberg *Deutsch med Wchnschr*, 1908, No 47

24 Hoffman *Kongress f inn Med*, 1902, xx

the heart, thus creating the impression of enlargement, which is in fact only a displacement. These observations have special point in connection with orthostatic albuminuria, in which all observers who have used the x-ray for determination of heart size have without exception failed to find the heart enlarged, as opposed to those who by percussion frequently found the opposite. A concrete example in one of our cases will illustrate this liability to error.

Case 4 is a boy aged 14 years, tall, rapidly growing, with the flat, narrow chest which we have found so frequently in these cases, and which appears to be accentuated at puberty. Careful examination shows an overacting heart, a somewhat diffuse apical impulse, heaving in character, the left border percussing one finger outside the nipple line.

Such a heart might on purely clinical grounds be considered enlarged. An orthodiagram, however, reveals a heart normal in shape and size, but one which, owing to the narrowness of the chest, appears to occupy more space than is allotted to the heart in a chest of normal capacity, it therefore appears nearer the axilla, the heart being relatively too large for the thorax. Exactly similar conditions obtain in Case 8, a tall narrow-chested 10-year-old girl. The same explanation will apply to our finding so many small hearts, they are absolutely smaller for the height of the child, but relatively to the narrow chest they are normal in size.

#### THE JUVENILE HEART

It appears, therefore, that the foregoing results fail to disclose any evidence of cardiac enlargement in the great majority of cases. The few exceptions, however, to one of which reference was made in an earlier part of this article, are worthy of careful consideration, because they illustrate a definite heart type which, both as to morphology and function, stands in marked contrast to the rest of our cases. These are Cases 9, 17 and 18.

Although only one of these (Case 18) shows orthodiagraphically a definite enlargement of the heart, there is undoubted evidence of left ventricular hypertrophy in all of them. Viewed on the fluoroscopic screen one is immediately impressed by the deliberate forcible pulsation of the left ventricle, by the rounded blunt apex and by the transverse position and oval shape which the heart has assumed (see Fig. 1 and compare with Fig. 2). These are all classical signs of left ventricular hypertrophy, combined in Case 18 with moderate dilatation. What is the significance of these changes in heart action and shape?

Under the name of "*Wachstumshypertrophie*" or juvenile heart, Krehl<sup>25</sup> has described a type of case in which an enlarged heart occurs at or about the age of puberty, in the absence of nephritis or other

<sup>25</sup> Krehl. Nothnagel's System, xv, 391.

usual cause of left ventricular hypertrophy In a large series of boys he was able to find a number in whom the heart was enlarged to percussion In others in whom no enlargement was demonstrable, there was distinct evidence, however, in the heaving impulse and in the accentuated basic sounds, of left ventricular hypertrophy In those cases in which the apex impulse was not heaving, although the heart percussed beyond the nipple, it was assumed that dilatation predominated over hypertrophy Some of these cases had subjective symptoms, others had none, but in Krehl's experience their presence in every instance was associated with the heart changes described

Our three patients above referred to, only one of whom complained of any subjective symptoms, correspond well to the Krehl type They



Fig 1—Orthocardiogram of "Juvenile Heart" Transverse diameter 1.5 cm greater than normal Shows transverse position, rounded apex, and deliberate, powerful pulsation characteristic of left ventricle hypertrophy

Fig 2—Orthocardiogram of normal heart

comprise a group in which probably only transitory heart changes occur, dependent on the disproportionate development of the circulatory organs and the rest of the body<sup>26</sup> In some cases this leads to an efficient hypertrophy, the heart being equal to the increased demands made on it In others this hypertrophy is insufficient and subjective symptoms develop

We are still more assured that these three cases correspond to the juvenile heart of Krehl, from the observations of Schwartz<sup>26</sup> The latter has made orthodiagraphic tracings of these hearts and insists that the fluoroscopic appearance above described is characteristic of this condition, and that by this means only can it be definitely diagnosed This is a point worthy of emphasis By the ordinary methods of heart

<sup>26</sup> Schwartz In von Jagie's *Handbuch der Herz und Gefässerkrankungen*, Vienna, 1912, p 436

examination the pure hypertrophy without cardiac enlargement in these cases might easily be overlooked, whereas the above-described characteristic heart silhouette effectively decides the diagnosis

#### EXAMINATION OF HEART RATE AFTER EXERTION

All who have written on the subject of orthostatic albuminuria are agreed that in the cases characterized by cardiovascular disturbances, the most constant feature is the variability of the pulse, its so-called "lability" (instability). By this term (German "*Labilität*") is understood the tendency of the pulse to become much more rapid and poor in quality after very slight exertion. In cases showing this phenomenon, after simple exercise, as running up and down a few flights of stairs, it may be impossible to count the pulse at the wrist, owing to its extreme rapidity and smallness. In its most marked form, change in posture

TABLE 3—PULSE RATE RECUMBENT, STANDING AND AFTER EXERCISE IN CASES OF ORTHOSTATIC ALBUMINURIA\*

Case	Pulse Rate in Recumbent Position	Pulse Rate Standing	Pulse Rate after Exercise	Case	Pulse Rate in Recumbent Position	Pulse Rate Standing	Pulse Rate after Exercise
1	68	72	124	16	72	80	144
2	78	80	100	17	68	72	136
3	92	92	184	18	120	120	148
4	92	96	160	20	112	124	156
5	76	76	72	22	76	88	84
6	80	100	152	23	84	100	88
7	78	86	128	25	100	100	96
8	88	100	108	26	80	84	100
9	88	88	132	27	80	80	160
10	96	104	144	30	120	120	120
11	80	84	148	31	88	96	132
12	96	120	172	32	80	112	150
13	100	104	?	33	80	88	96
15	140	140	195	34	80	80	168

\*Cases 1 to 15 are those which show cardiac symptoms or physical signs

from the recumbent to the upright is said to result in a disproportionate rise in pulse-rate. To this symptom Thomayer gave the name "orthostatic tachycardia." Fischl<sup>13</sup> found this instability to be an almost constant symptom, the pulse becoming smaller and more rapid by 25 to 30 beats, while Pelnar<sup>27</sup> in sixteen cases was able at times to note an actual doubling of the pulse-rate. The effect on the pulse of the change of position from the horizontal to the upright is of special interest, because the albuminuria in these cases is so closely related to posture.

In Table 3 in the first column are given the pulse-rates in the reclining position. The rates resulting from a change to the upright position are seen in the next column. These figures show in the first place

27 Pelnar Centralblatt inn Med, 1905, p 1025

that practically all the patients have approximately normal heart-rate when resting. The increase in rate on standing in the entire group varied between 0 and 32 (average 7). In the cases showing cardiovascular disturbances the increase varied from 0 to 24 (average 7). It will be seen that the cases showing symptoms differ in no wise from the remainder of the group of albuminurics. We have as a control examined the pulse-rates in ten perfectly healthy normal children 9 to 14 years of age, and found that the rate after changed positions was increased from 0 to 16 beats (average 8.4), in other words, slightly greater increase than in albuminurics. The increase in rate in our cases of albuminuria can therefore in no manner be considered excessive.

There are also numerous figures available for comparison in the literature. Dietlen<sup>28</sup> in adults finds a normal variability of 8 to 40 beats, with an average of 18, Guy<sup>29</sup> found a range of 4 to 44 and Shapiro<sup>30</sup> 10 to 30 beats. It is therefore evident that our cases do not show any marked instability on change of posture. We have no doubt that unusual environment and the nervousness attendant on it, which we have taken pains to eliminate, can easily lead to error, as those hearts which at rest are unduly rapid show a proportionate increase on change of posture.

In the third column of Table 3 are tabulated the pulse-rates after exercise, which consisted in running up and downstairs, as noted before. The average increase in the cases with cardiac disturbance is 48 beats per minute, whereas, in the remainder the pulse-rate increased but 22 beats per minute. Results such as this would at first glance seem to point clearly to an abnormal irritability of these hearts and would seem to correspond well with the description given by the Germans to cases of pulse instability. However, when we examined the pulse-rates in perfectly normal children used as controls, we were much surprised to find that in them the increase in rate even exceeded that occurring in the orthostatic albuminuria cases, the healthy children showing an average increase of 50 beats per minute. Mere numerical increase in pulse-rate, therefore, cannot be taken as a criterion of instability in these cases.

From all the foregoing it might be suspected that our cases are in reality not of the same class as described by Martius as dilatative weakness, since we have shown that both as to heart size and pulse-rate our results are not in accord. However, when we take into account the character of the pulse before and after exertion, and especially when we compare the pulse with the cardiac action, both as evident to inspection and to the *x*-ray, we are impressed by the fact that our cases and those of Martius are the same. A large percentage of our patients after run-

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28 Dietlen *Deutsch Arch f klin Med*, 1909, xcvi

29 Guy *Guy's Hosp Reports*, 1838

30 Shapiro *Wratsch*, 1881 (quoted by Dietlen)



ning the stairs presented a characteristic picture of extreme fatigue and dyspnea. The pulses, which had previously been fairly strong, became weak and thready, so that in several instances the pulse could not be counted at the wrist. At times irregularity of the pulse also occurred. Not only was the apex impulse in many of these children with weak pulses extremely forcible, but the x-ray revealed markedly overacting hearts. This paradoxical condition of pulse and apex, which has been so frequently emphasized by European observers, therefore appears to be a characteristic symptom of this condition.

#### EXAMINATION OF THE SHAPE OF THE HEART

Aside from the information we have acquired concerning the size and functional capacity of the heart, x-ray study of our cases has revealed some interesting features concerning heart shape. It is well known from

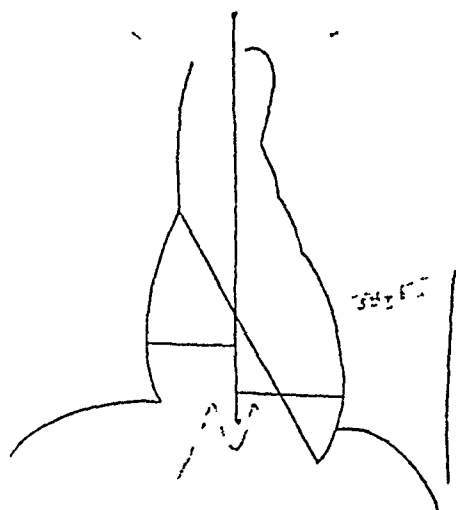


Fig 3—Orthocardiogram of "Drop Heart." Transverse diameter 8.8 cm. Normal is 12.5 cm. Note position of fifth rib.

the works of Veith and Reyher<sup>31</sup> that the commonest form of the heart silhouette in childhood is that of an obliquely placed oval (Fig 2), less commonly hearts of a rounded shape occur, and still more rarely the heart assumes either a transverse or a vertical position. The study of the heart shape in our cases shows in quite a number a striking deviation from this normal type. This abnormality consists in the tendency that the hearts show to assume a more median position in the chest, the apex of the organ appearing relatively lower, thus causing a vertical position of the heart axis. This gives the heart a drawn-out, narrow appearance, which, coupled with the elongation of the great vessels, results in a distinctive heart picture which has been aptly termed by the Germans the drop heart (*Tropfenherz*). This condition (Fig 3), or one closely

31 Reyher. *Jahrb f Kinderh*, 1906, lxiv.

approaching it, we have found in ten of our cases, about 30 per cent, contrary to the report of Fischl,<sup>13</sup> who was unable to find such hearts in cases of orthostatic albuminuria

The drop heart has for many years been well known to the Germans, especially through the writings of Kraus,<sup>32</sup> by whom it has been associated with narrow-chested individuals, showing the neurasthenic habitus, who reveal various stigmata of constitutional weakness in which the heart is supposed to participate. Our findings, therefore, of such a large percentage of vertical or drop hearts is of particular interest, in view of the fact that it occurs in the very type of child which Martius has characterized as constitutionally weak

### CONCLUSIONS

Reviewing briefly the results of our investigations, we believe the following conclusions are warranted

1 In a series of cases of orthostatic albuminuria selected at random, it will be found that a considerable number present evidence of relative cardiovascular insufficiency

2 These symptoms, in the great majority of cases, are not associated with any hypertrophy or dilatation of the heart. On the contrary, the heart is in many cases smaller than normal, nor does it show any gross evidence of weakness as dilatation after exercise, an explanation suggested by previous investigators

3 Although the hearts do not dilate after exercise, a considerable number of them fail to become smaller under these conditions. This failure to contract may perhaps be looked on as a restriction of the field of cardiac response

4 The condition known as the juvenile heart or "*trophie*" occurred three times in our cases and recognized

5 The conception of pulse or heart m  
a tendency of the pulse to become palp  
a condition which we have found very

6 In 30 per cent of the cases we have hearts of  
especially associated with other stigmata  
ment

In conclusion we wish to express our  
department of Mount Sinai Hospital for  
during the course of our work

54 West Ninety-First Street—122

## A PRELIMINARY REPORT ON THE EFFECT OF STRYCHNIN AND DIGITALIS ON MAN\*

DAVID MARVIN, M.D.

BURLINGTON, VT

It is not the object of this article to enter into a discussion of the effect of strychnin or digitalis on the systems of the body as observed on the lower animals, or to go over the literature on the subject, but to report observations when these drugs were administered in therapeutic doses to normal young men

Before entering on a report of the findings, I desire to call attention to the fact that text-books on pharmacology and highly scientific articles pertaining to this subject are based largely on experimental evidence furnished by the lower animals. This evidence has been and is of inestimable value in determining the presence and the location of an effect and establishes a valid reason for a continuance of the experimental work by making observations on the higher animal, man.

In a very few instances observations have been made on the normal man and the effect as seen has been reported. In nearly all cases, however, such observations have been on a single case or on a number of such cases under different conditions, thus making the results of little value. It is only when conditions are identical that a composite curve becomes of value. I question the advisability of accepting in all cases the evidence of an effect on respiration, pulse and blood-pressure furnished by the lower animals as satisfactory proof of a similar action in man. I have arrived at this conclusion after careful observations of the effect of some of our most important drugs on groups of men and a comparison with the scientific findings on animals.

I am inclined to believe that this may be the main reason why pharmacologists and clinicians have held opposite views regarding important drugs, the pharmacologist furnishing conclusive scientific proof of action as based on the lower animals, while the clinician has failed to furnish the necessary scientific proof on the diseased man.

I think that the time is at hand when pharmacologists should establish scientific proof of the effect of important drugs when administered in different doses on the normal man, not that we can infer that a similar action must necessarily follow in the diseased man, but, from the

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evidence thus furnished, we will be in the best possible position to study the effect on the diseased man, compare the results and determine wherein they differ. Until this evidence is forthcoming we cannot expect that pharmacology will be placed on a highly scientific basis.

## STRYCHNIN

Strychnin and digitalis are two important drugs, the effect of which seems to have been in doubt, as voiced by both pharmacologists and

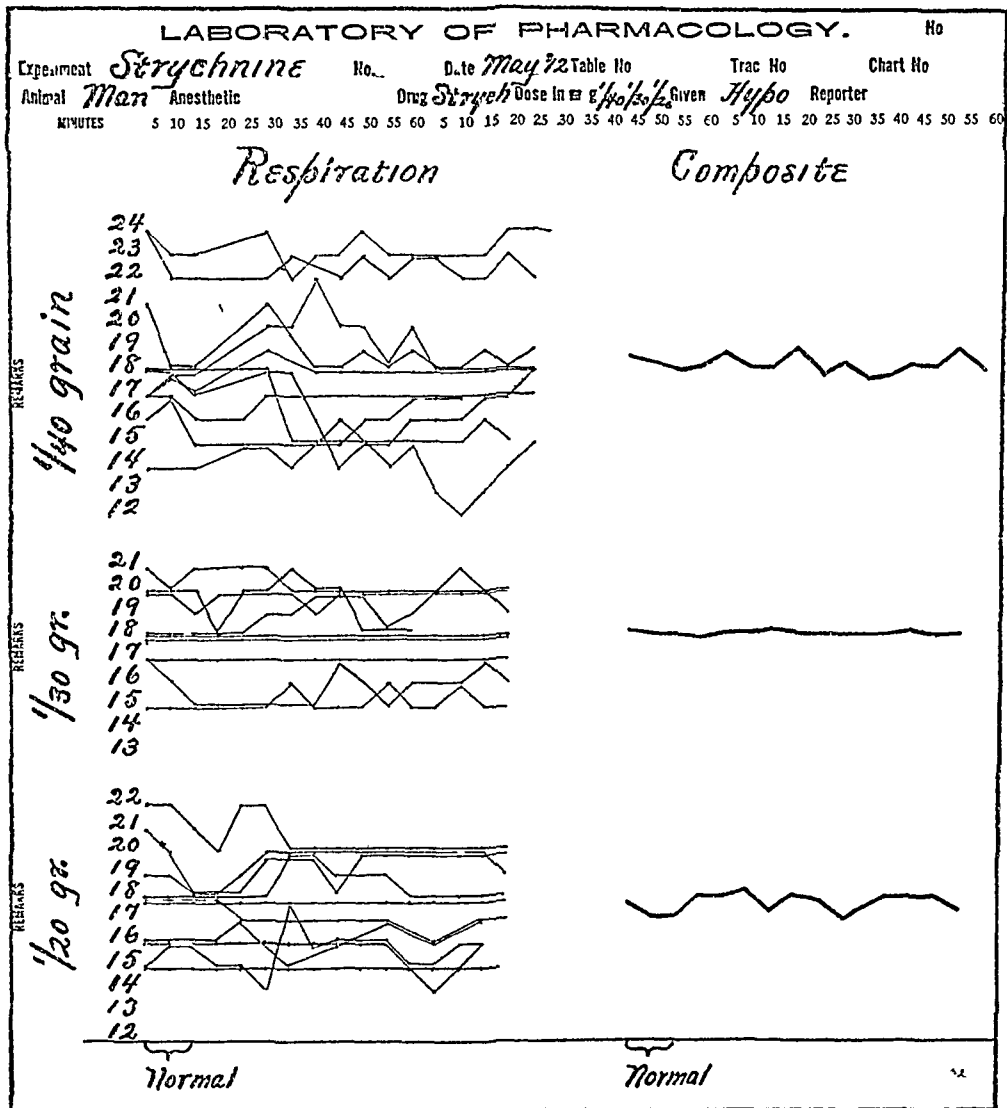


Chart 1—Curves showing the effect at various time intervals of strychnin in different doses on the respiration

clinicians, the majority of pharmacologists claiming that strychnin and digitalis do not increase blood-pressure while some clinicians claim to have seen such effect. In view of this fact and the desire to add to the evidence, I submit the following observations made on groups of medical students in the University of Vermont who willingly volunteered their services. Selection was made to exclude those who were under the

influence of nicotin They were all seated at tables in the laboratory and remained very quiet throughout this entire experiment, thus making the conditions identical About twenty minutes were allowed to elapse before beginning observations, thereby permitting respiration, pulse and blood-pressure to return to normal Three normal observations were then taken The respiration and pulse were taken by students of the section who were not taking the drug, while the blood-pressure in all cases was taken by my assistant or myself

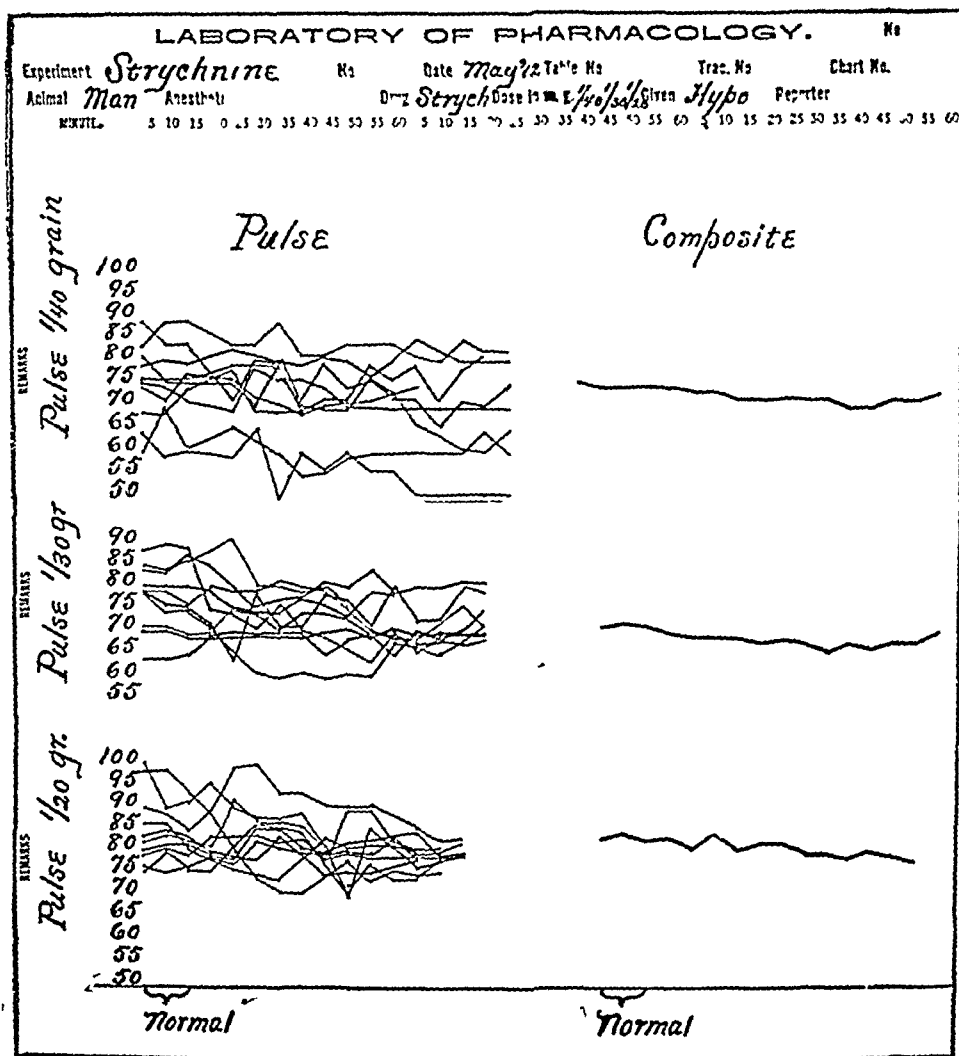


Chart 2—Curves showing the effect at various time intervals of strychnin in different doses on the pulse-rate

After completing the normal observations, strychnin sulphate was injected by hypodermic into the muscular tissue of the upper arm Observations were then made every five minutes on respiration and pulse and every ten minutes on blood-pressure

These experiments were conducted on three different days, each time using a different dose of strychnin sulphate

June 3, 1912, at 9 13 a m, ten men of Section A received 1/20 grain.

June 5, 1912, at 11 25 a m, ten men of Section B received 1/30 grain

June 22, 1912, at 11 15 a m, ten men of Section B received 1/40 grain

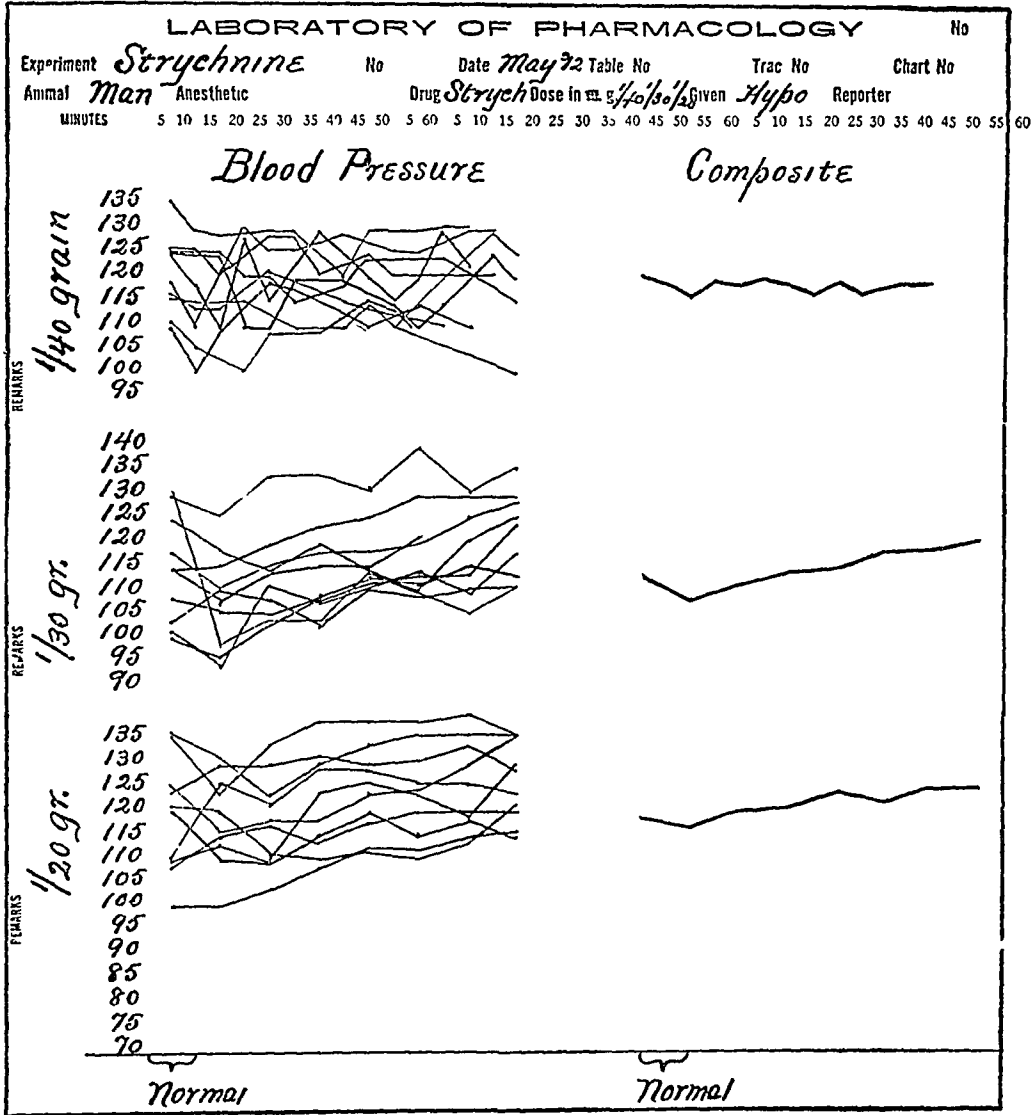


Chart 3—Curves showing the effect on blood-pressure of different doses of strychnin

Nearly all who received 1/40 grain were men who did not receive the drug on June 5

The result of these experiments seems to indicate that strychnin in doses of 1/40, 1/30 and 1/20 grain has no appreciable effect on the rate of respiration (Chart 1) There is an average slowing of the pulse-rate of five beats per minute from 1/40 grain, seven beats per minute from 1/30 grain and eight beats per minute from 1/20 grain (Chart 2) The maximum effect from 1/40 and 1/30 grain seems to have been reached

at the end of forty minutes, while from 1/20 grain the composite curve shows a downward tendency at the end of the experiment.

The blood-pressure curve, taking the last normal observation as our standard, shows an increase of about 3 mm of mercury from 1/40 grain, 13 mm from 1/30 grain and 8 mm from 1/20 grain.

It will be noted from the graphic chart (Chart 3) that there was a slight increase in blood-pressure from 1/40 grain, a pronounced increase

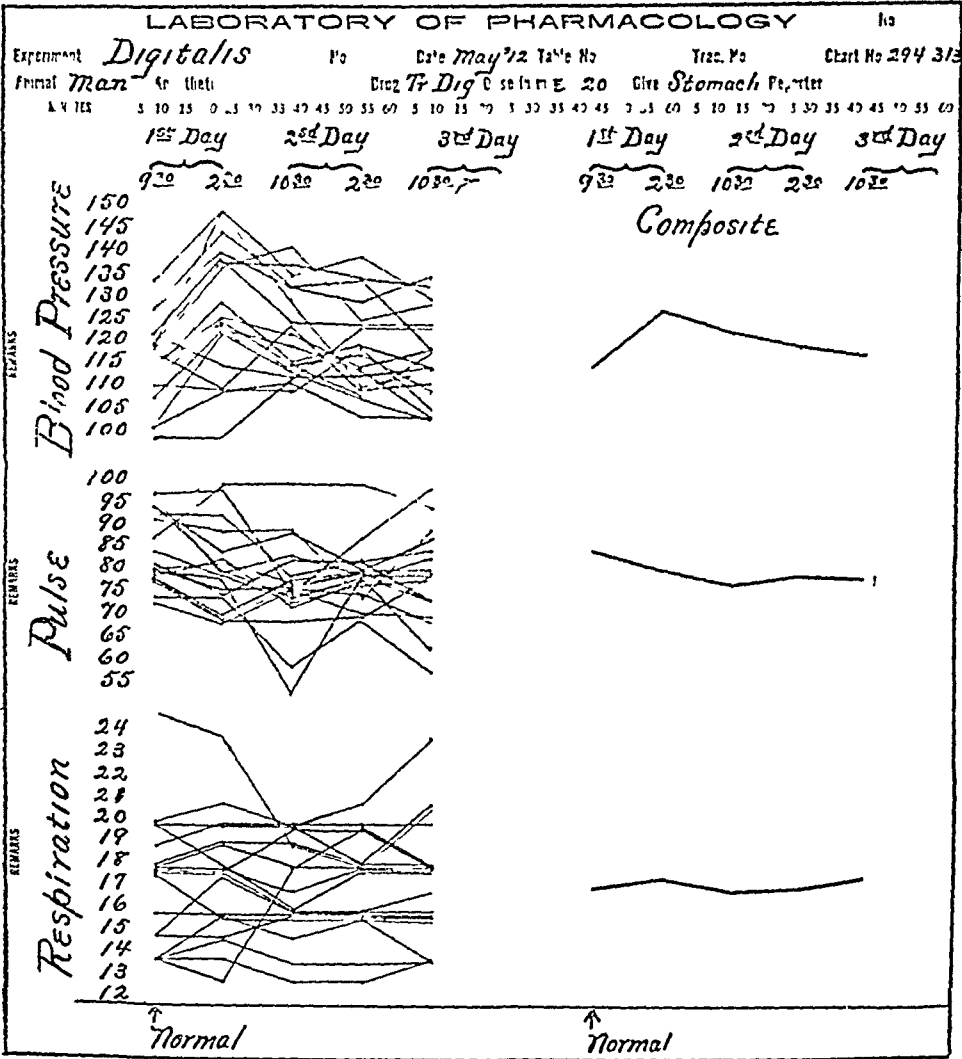


Chart 4 —Curves showing the effect of digitalis on respiration, pulse and blood-pressure

from 1/30 and 1/20 grain and at the end of the experiment, the blood-pressure was increasing

I believe that this evidence, obtained from thirty observations with varying doses, is conclusive proof that strychnin, when given in the above doses by hypodermic injection, does increase blood-pressure in the normal man

A former series of similar experiments conducted in like manner, with the exception of the method of administration, the strychnin being given under the tongue, produced identical results. The duration of effect was shorter, the blood-pressure returned to normal in forty minutes from 1/30 grain and in one hour from 1/20 grain.

#### DIGITALIS

From experiments on groups of men conducted in like manner as in the strychnin experiments, we have failed to obtain any effect on the rate of respiration or pulse or any change in blood-pressure during one hour and twenty minutes following the administration of tincture digitalis.

The doses were 10, 15 and 20 minims, given by stomach.

These results were anticipated from the knowledge of the active principles present in digitalis and the consensus of opinion as to the time after its administration before an effect is supposed to occur.

Having thus failed, we determined to conduct an experiment with a group of men, taking observations twice each day. The object of this experiment was, first, to establish the presence of an effect, if any, from a single dose, and second, if an effect was noticed, to determine how long it continued.

The preparation used during these experiments was a fresh tincture made from Allen's English leaves on April 12, 1912, by W. H. Zottman & Co. of this city. After obtaining results from this tincture, I desired that it be standardized by a disinterested person, using the same methods as are used by the large manufacturers. Mr. P. S. Pettenger of the H. K. Mulford Co. kindly volunteered to standardize it on guinea-pigs, which he did, finding it to be a 6.9 per cent tincture. From this we conclude that the dose of 20 minims given was equivalent to about 14 minims of a standard tincture. Therefore the results obtained should be considered as produced by 14 minims instead of 20.

A group of men were selected on May 20, 1912, under similar conditions as in the strychnin experiments, and, after obtaining the normal observations, they were given at 9.30 a. m. 20 minims of the above tincture digitalis.

At 2.30 p. m. on the same day, after this group had listened to a lecture for one period, and, from previous instructions, had remained quiet in their seats, observations were repeated on respiration, pulse and blood-pressure.

These observations were repeated on May 21, in the same room and under identical conditions, at 10.30 a. m. and 2.30 p. m., also on May 22 at 10.30 a. m.

The observations on respiration and pulse were made by students, while all observations on blood-pressure were made by myself.

A change in the schedule of this group on the afternoon of May 22 interfered and observations were not made until May 23 at 10.30, when



the average blood-pressure was found to be normal This last observation is excluded from the graphic chart

After a careful study of our findings, I determined to repeat the experiment under similar conditions, but with a different group of men and have Dr. Bush, my assistant, take all observations on blood-pressure, that he might disprove or verify my findings This was done on May 27, 28 and 29

The results from this group were found to correspond with our first group, as will be seen from the graphic chart which represents all observations (Chart 4).

It will be noted that an average increase in blood-pressure of 13 mm Hg occurred, which reached its height in five hours, and that it did not return to normal until after fifty hours had passed.

This increase occurred in seventeen out of eighteen cases, and in thirteen the greatest effect was noticed at the end of five hours, thus proving that the old idea of the maximum effect appearing in twenty-four hours is erroneous

A slowing in the pulse of eight beats per minute was obtained with practically no effect on rate of respiration

Controls were used in all these experiments, which show little or no variation from a straight line Such slight variation as occurred did not conform to the composite curve showing drug effect

I regret that the strychnin experiments were not conducted over a longer period of time, that the maximum height in blood-pressure and its duration could have been determined, but this was made impossible by our schedule It is my purpose to conduct further experiments in the near future with this idea in view

#### SUMMARY

##### STRYCHNIN

No effect on the rate of respiration, except from 1/20 grain, which produced an average increase of one per minute This effect was not constant, a drop occurred occasionally, which was due largely to individual fluctuations occurring at the same time and without apparent cause

A slowing of the pulse-rate from all doses

A marked increase in blood-pressure from 1/30 and 1/20 grain  
Practically no effect from 1/40 grain

##### DIGITALIS

No effect on the rate of respiration

A slowing in the pulse-rate of eight beats per minute

A marked increase in blood-pressure which reached its maximum in five hours, gradually returning to normal after fifty hours

A persistence of action for fifty hours from a single dose of 14 minims of a standard tincture digitalis

# HUMAN BOTRYOMYCOSIS OF THE LIVER<sup>1</sup>

EUGENE L. OPIE, M.D.

ST. LOUIS

The disease of horses subsequently known as botryomycosis was first described by Bollinger<sup>1</sup> in 1870. He found multiple grayish-white fibrous nodules in the lung of a horse. Areas of softening occurred within the nodules and in the pus were yellow white granules which were just visible and resembled the yellow granules of actinomycosis. Examined under the microscope these granules do not exhibit the characteristic appearance of the "ray fungus," but are composed of coccus-like bodies surrounded by a homogeneous medium, which, regarded as a capsule, collects the microorganism into a zooglea mass. On the surface of the granule are rounded projections which give it a mulberry-like form. A disease characterized by the presence of this microorganism is not uncommon in horses and in some countries, particularly in the tropics, affects the human skin. The disease in man has not been described in this country and in none of the instances observed elsewhere has it attacked an internal organ.

Botryomycosis is described in text-books of veterinary medicine.<sup>2</sup> It occurs occasionally in cattle and swine. Several writers make the statement that actinomycosis is not uncommon in cattle and infrequent in the horse, whereas, the similar lesion of botryomycosis is frequent in the horse and uncommon in cattle. Firm nodules are formed in the skin, particularly in regions where it is subjected to continued rubbing of the harness, for example, below the collar, and after the skin has broken and pus is discharged, infection is transferred to other parts of the skin exposed to like friction, the microorganism being, presumably, rubbed into the ducts of cutaneous glands. Infection of wounds occurs and the development of a slowly growing fibrous tumor or botryomycoma has been repeatedly observed in geldings at the site of the cut end of the spermatic cord. Botryomycosis occurs in organs not obviously exposed to infection, for example, the udder.

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\* Accepted for publication in THE ARCHIVES, Jan. 31, 1913.

\* From the Department of Pathology, Washington University Medical School, St. Louis.

1 Bollinger. Mycosis der Lunge beim Pferde. Virchows Arch. f. path. Anat., 1870, xlix, 583.

2 Huttyra and Marek. Pathology and Therapeutics of the Diseases of Domestic Animals (Translation). Chicago, 1912. Kitt. Lehrbuch der pathologischen Anatomie der Haustiere. Stuttgart, 1906-1910.

The newly-formed mass of fibrous tissue is usually situated in the subcutaneous tissue, but may extend into the muscles. Tumor-like masses, weighing from 30 to 60 pounds, are described. The lesion arising at the cut end of the spermatic cord may extend along the inguinal canal to the peritoneum. The swelling consists, in large part, of dense fibrous tissue, but all the elements of an infectious granuloma, including epithelioid and giant cells, are represented. Formation of pus occurs particularly about the colonies of microorganisms, and fistulous suppurating canals often penetrate the lesion and open on its surface. Numerous nodules may be formed in the skin near the primary lesion. Regional lymphatic nodes may enlarge and form foci of suppuration, but more frequently the lymphatics and lymphatic nodes are unaffected.

Botryomycosis of the horse occasionally occurs in the internal organs and is usually secondary to infection of the skin or of a wound. Primary botryomycosis of internal organs has been observed rarely. Secondary nodules have been found in the kidneys, liver and spleen, in bones and in other organs usually in association with infection of the spermatic cord. Simultaneous development of the lesion in a number of organs has been observed in several instances.

Peculiar to botryomycosis are the minute yellowish-white lobulated or mulberry-like granules composed of cocci held together by a homogeneous material which is often conspicuous as a clear layer at the periphery of the body, the whole having the appearance of a colony of micrococci. W. Ernst<sup>3</sup> points out that the smallest masses of cocci are not surrounded by the encapsulating material which stains with acid dyes such as eosin or picric acid, but form this material at a later stage. The rounded projections on the surface of these bodies giving them their mulberry-like form are produced by multiplication of cocci within the capsule, distending and rupturing it at certain points, for in favorable sections he found bacteria uncovered by the homogeneous material projecting through this otherwise intact medium.

To the peculiar colony-like structure which has been described, Bollinger, finding it in the lung, gave the name *Zooglea pulmonis equi*. Rivolta<sup>4</sup> subsequently rediscovered the same microorganism in a tumor from the cut spermatic cord of a horse, and considering it analogous to *Actinomyces*, gave it the name *Discomyces equi*. John<sup>5</sup> found the microorganism in a fungoid growth from the spermatic cord of a horse and in nodules of the skin, and recognizing its coccus form, called it *Micrococcus ascoformans*. In 1886, Rabe<sup>6</sup> first described cultures and inoculation

3 Ernst, W. Centralbl. f. Bakteriologie, 1908, xlv, Part 1, 121.

4 Rivolta. Giorn. di anat. e fisiolog., 1884, x, 10. Quoted by Baumgarten.

5 John. Ber. über d. Vet. in Königl. Sachsen für 1884, Dresden u. f. 1886 and 1887. Quoted by Galli-Valerio.

6 Rabe. Deutsch. Ztschr. f. Tiermed., 1886, xii, 137. Quoted by Galli-Valerio.

experiments made with material obtained from the lesions of the horse. The micrococcus which he obtained formed silvery gray colonies, and these later assumed a yellow tint, an opaque yellow layer developed on potato. Stabbed into gelatin what was regarded as a characteristic change occurred; about the line of inoculation there was feeble liquefaction, a cup-like cavity shaped like a tulip being formed near the surface. All cultures had an odor recalling that of strawberries. No capsule resembling that seen in the tissues was formed in cultures. Inoculation into small animals caused immediate death or formation of an abscess. In the horse, however, a tumor similar to that which occurred spontaneously was produced at the site of inoculation and contained the characteristic capsulated masses of micrococci. Rabe named the microorganism *Micrococcus botryogenes*. Similarly successful inoculation experiments have been performed by Kitt,<sup>7</sup> de Jong<sup>8</sup> and others, but the distinctive cultural characters described by Rabe have not been confirmed.

Kitt regards the organism as a variety of *Staphylococcus pyogenes aureus*. Galli-Valerio,<sup>9</sup> who has studied the cultural characters of an organism obtained from a typical human lesion of the skin containing characteristic masses of cocci, has found no distinctive cultural peculiarities and agrees with the view of Kitt. Poncet and Dor<sup>10</sup> first isolated the organism from a human lesion of the skin and produced on the udder of a she-ass a pedunculated growth which was not examined microscopically, they regard the microorganism as a distinct species. Baumgarten<sup>11</sup> expresses the view that the microorganism is undoubtedly a distinct species belonging to the same group as *Staphylococcus pyogenes aureus*, but regards as distinctive its capacity to form within the tissues a gelatinous membrane about colonies of cocci. This view being accepted, the term botryomyces is not applicable to the microorganism. The name botryocycosis applied to the disease is, like actinomycosis, firmly established in the literature of the subject.

The following case is described because, in the first place, doubt has been expressed concerning the occurrence of botryomycosis in man (see section on pseudobotryomycosis). The case, moreover, is apparently the first recorded instance in which the disease in man has attacked an internal organ, in this instance the liver. Since the disease, it appears, has not been observed in this country, the case may direct attention to

7 Kitt. Centralbl f Bakteriöl, 1888, III, 177. Monatsch f prakt Tierheilk.

8 De Jong. Diss. Giessen, 1899. Quoted by Baumgarten 1890, I, 148.

9 Galli-Valerio. Centralbl f Bakteriöl, 1902, XXXI, Part I, p. 508.

10 Poncet and Dor. XI Congr. français de chirurgie, Paris, 1897, Lyon méd., 1897, No. 43, p. 213 and 1898, No. 5, p. 145, Arch. gen. de méd., 1900, III, 129, 274. Quoted by Galli-Valerio.

11 Baumgarten. Lehrbuch der pathogenen Mikroorganismen, Leipzig, 1911.

other instances of the same condition There is no complete record of the autopsy performed on the patient Unfortunately no cultures were made at the time of autopsy

#### CASE REPORT

The patient, a girl aged 11 years, from Sabula, Mo., was admitted to the St. Louis Children's Hospital Aug 27, 1910, in the service of Dr. George M. Tuttle, who has kindly permitted me to make use of the accompanying history

*History*—The mother of the child is said to have died of tuberculous pneumonia She has a father and one sister in good health

In the spring over one year before her admission the patient had scarlet fever and has not been well since that time She has been losing weight and strength since last November, when she is thought to have had malaria Her appetite has been poor and at times she has had fever She has had severe pain in the abdomen and there has been pain at times in the right side, at times in the left

No horses in the vicinity are known to have been diseased The patient received milk from a neighboring farm, one cow of the herd showed signs of sickness during the fall and died the following spring "with a wasting disease that affected her water"

*Examination*—On admission the patient was a well developed girl but weak and emaciated, having the appearance of a child much older than her real age The skin was jaundiced and dry and the superficial veins were everywhere much congested Over the body there was desquamation of the epidermis, and scattered, numerous small ulcers about the size of a pin's head

The entire epigastric region was distended by what appeared to be a hard, irregular mass continuous with the liver and extending into the left hypochondriac region The edge of the liver was thin, extended a half finger's breadth below the costal margin in the mammary line and approached to within about a centimeter of the crest of the ilium in the axillary line There was marked rigidity and tenderness over the entire abdomen, most severe in the epigastric region and in the neighborhood of the left kidney where the pain was so severe that palpation was impossible

Respiration was rapid, 40 to the minute, and very shallow With deep respiration there was pain referred to the swelling in the epigastrium The intercostal spaces, the depressions above and below the clavicle, and the supra-sternal notch were much depressed There was well-marked bulging of both sides of the chest at its base, more marked on the right side Auscultation and percussion gave no noteworthy information The apex beat of the heart was displaced to the left and was found just outside the nipple line

While in the hospital the patient gradually became weaker Her appetite was fairly good She passed copious soft white or yellow stools A stool examined August 31 was grayish-white and contained fat crystals in abundance, there were no bile pigments

The temperature was invariably between 97 and 98.8 C save on the second and third days after admission (100) and on the third day before death (100)

The blood examined on August 29 contained 3,272,000 red blood corpuscles, 60 per cent hemoglobin and 28,400 leukocytes

The urine while the patient was in the hospital has the following characters Specific gravity, 1.008 to 1.015, albumin, present, bile pigments, present, sugar, absent, there were granular casts and a few leukocytes

The patient became unconscious on the morning of September 8, and died with slow, gasping respiration three hours later

*Necropsy*—A necropsy was performed by a hospital intern A note stated that more than half of the liver substance was involved by a tumor like lesion which was firm and contained cyst-like cavities filled with pus Similar abscesses were found elsewhere There was hydrops of the gall-bladder Only the liver, which was put in Kaiserling's solution, was preserved

Liver On the upper surface of the liver near the posterior border below and on either side of the falciform ligament is a large, irregular, puckered area approximately 10 cm across, where the tissue has a deep yellow color broken by grayish depressed spots. At the margin of this area surrounding it are low rounded

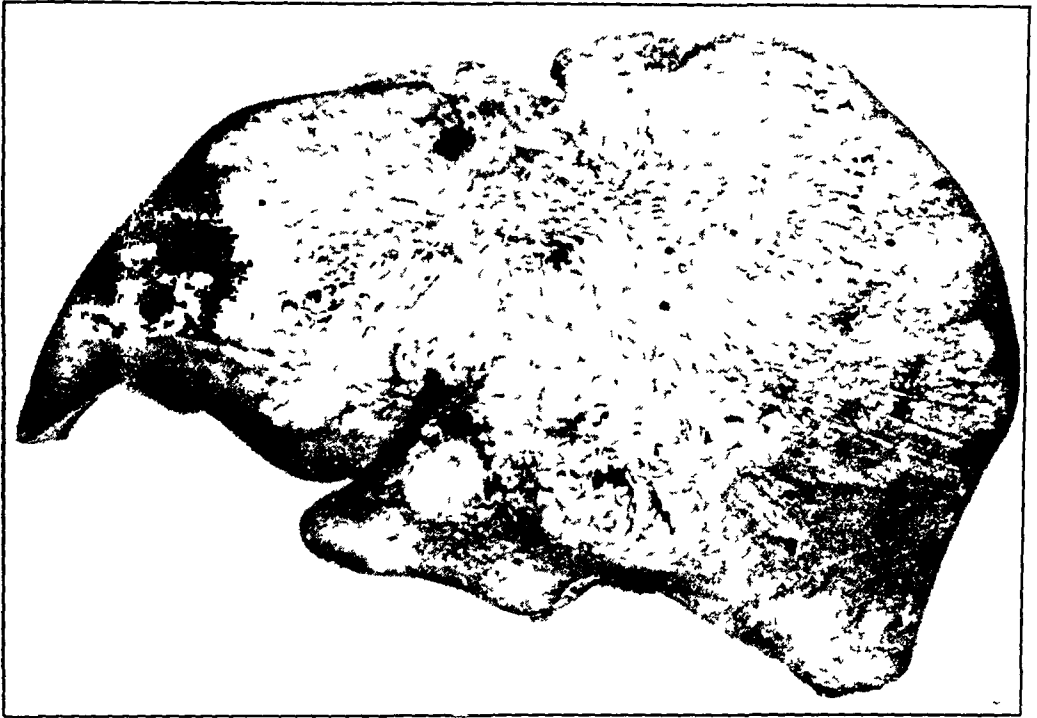


Fig 1—Photograph of the cut surface of the liver with botryomycosis. The center of the lesion consists of fibrous tissue, in the periphery are abscess cavities.

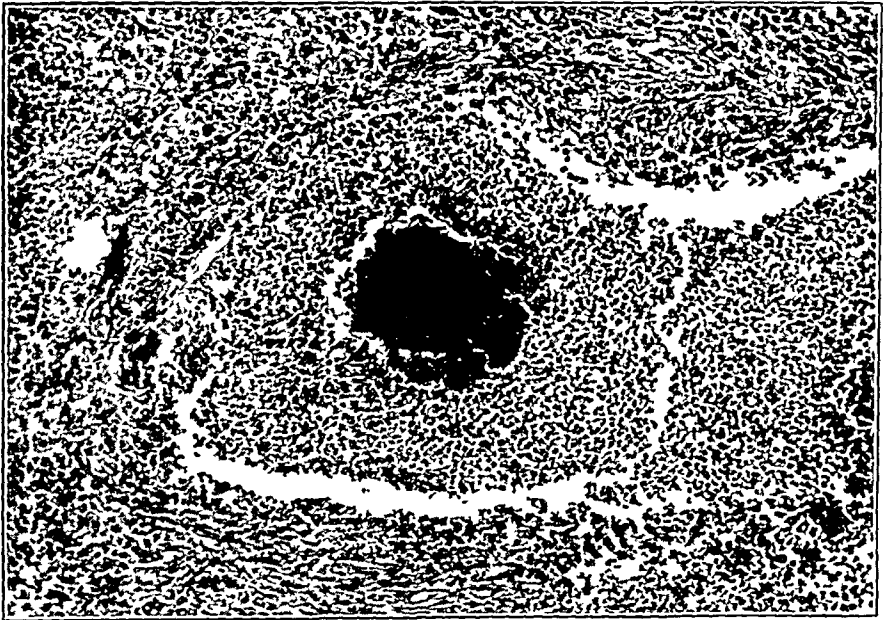


Fig 2—Microphotograph showing a botryomycotic granule surrounded by pus and within a cavity the wall of which is formed by newly-formed fibrous tissue.

confluent elevations of the liver substance often 2 or 3 cm across. The centers of these elevations are soft, have a yellowish tint and correspond to abscess cavities in the underlying tissue. The surface of the liver near these abscesses shows in places bluish red discoloration. Remains of adhesions are attached to

the surface of the liver at the site of the lesion. Section made transversely through the liver (Fig 1) shows that an immense tumor like mass has replaced the greater part of the substance of the organ. The cut surface of the lesion has an irregularly semicircular form with its base corresponding to the upper surface of the liver. Bands of fibrous tissue radiate from the central part of the base which is represented by the irregular puckered area seen on the upper surface of the organ. The tissue composing the lesion varies in different parts. Immediately below the puckered superficial area just mentioned there is a narrow,



Fig 3—Drawing showing a botryomycotic granule composed of coccus like bodies held together by a homogeneous substance which forms a capsule

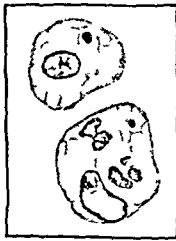


Fig 4

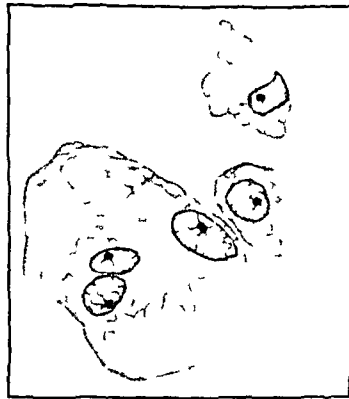


Fig 5

Fig 4—Drawing showing phagocytic cells containing droplets of fat

Fig 5—Drawing showing large fat containing cells which occur in large number within the newly formed fibrous tissue

irregular zone of tough, fibrous tissue. The tissue below occupying the center of the lesion is firm and consists of opaque yellow material broken by numerous fibrous bands which in general radiate toward the periphery of the lesion. Further outward the tissue is less dense and there are numerous small cavities filled with soft purulent material. In some places the cavities form irregular, elongated

communicating channels or sinuses separated by dense fibrous tissue. At its periphery the lesion has a honey-combed appearance and in places there are large abscess cavities. The largest of these cavities is 2 cm across, it is filled with soft yellowish pus and is lined by yellowish membrane about 0.5 mm in thickness. On section not more than one-third of the area is represented by normal liver tissue. In this liver tissue lobulation is obscure and there is a greenish tint as if due to jaundice. In the right lobe of the liver outside of the main mass of the lesion are two large portal spaces within which is an elongated channel with opaque yellow wall containing purulent material. Scattered in the remainder of the lobe are minute abscesses collected together in several groups.

The gall-bladder was found at autopsy to be distended, but otherwise showed nothing noteworthy.

*Microscopical Examination of Liver*—The liver substance is replaced by masses of dense fibrous tissue in which are cavities containing polynuclear leukocytes and other cells surrounding conspicuous masses of coccus-like bodies (Fig 2). The fibrous tissue varies considerably, being in places dense and poor in cells, elsewhere loose in texture and richly infiltrated with cells. In this connective tissue occur masses of large cells distended with fat and so abundant that they give to the tissue the yellow color mentioned above. The size of the abscesses and sinuses which contain the colonies of microorganisms varies greatly, and in the older parts of the lesion there are wide channels containing leukocytes and surrounded by fibrous walls rich in cells. There is no abrupt line separating the lesion from the liver tissue which persists. Liver cells at the margin of the lesion are compressed, atrophic and often contain abundant brown yellow pigment. Thickened strands of fibrous tissue separate these cells and in the adjacent relatively normal liver substance fibrous tissue of the portal spaces is considerably thickened.

*Botryomycotic granules* vary in abundance and size in different parts of the lesion. Three masses, each visible to the naked eye in the stained specimen, the largest being approximately 1 mm in length, are grouped together in one field of the low power (Obj 3, Oc 1). These masses are composed of bodies resembling staphylococci (Fig 3) which stain deeply with either hematoxylin or methylene-blue. At the edge are the irregular rounded projections which give a mulberry-like form to the entire mass when examined in fresh pus. In some instances the larger bodies in section appear to be separated into several isolated masses. Micrococci appear to be less densely packed together at the center of the mass, which stains less deeply than the outer part. Between the cocci is what appears as a homogeneous background which stains with eosin or picric acid (van Gieson's stain). In many instances particularly about the larger bodies, this homogeneous material is conspicuous at the edge forming a kind of capsule separating the cocci from the leukocytes about. The distinctness with which this clear zone can be made out varies much, in places it may be wholly lacking. The cocci exhibit some variation in size and particularly at the margin of the colony minute microorganisms are found.

Immediately about the botryomycotic granules polynuclear leukocytes occur in large number (Fig 2). Adherent to the surface of the mass red blood corpuscles are frequently seen. In most instances it is obvious that the botryomycotic granule lies in a small abscess cavity surrounded by pus, for in its immediate neighborhood tissue has disappeared and the purulent exudate (in the hardened tissue) has occasionally retracted from the surrounding wall of fibrous tissue. Leukocytes are usually well preserved, but in places a moderate number have lost their nuclei and are in process of disintegration. Polynuclear leukocytes which have ingested coccus-like bodies similar to those which form the colonies are not infrequent. Scattered cocci are occasionally found outside of cells, but in such instances the leukocytes in the immediate neighborhood are in part necrotic.



The wall of the abscess is formed by fibrous tissue containing numerous cells. In contact with the cavity are large cells with large oval or slightly irregular vesicular nuclei and abundant protoplasm. These cells (macrophages) are phagocytic and contain within their substance red blood corpuscles, nuclear fragments and remains of cells, still recognizable as polynuclear leukocytes (Fig 4). They occasionally contain cocci similar to those which form the colonies. The regularity and thickness of this zone of mononuclear cells varies greatly. The loose fibrous tissue in the wall of some large abscess cavities is thickly infiltrated over a wide area with cells having the characters just described. Many of these cells are of very large size, four or five times the diameter of a polynuclear leukocyte and distended with the remains of many ingested cells, some of which are still recognizable as polynuclear leukocytes. Similar cells are, in places, vacuolated, vacuoles being formed by fat recognizable by the usual reactions.

In places the connective tissue, perhaps in contact with the zone of phagocytic cells surrounding an abscess, is closely packed with very large cells, whose protoplasm is replaced by vacuoles. These vacuolated cells occurring in the meshes of loose fibrous tissue give it some resemblance to adipose tissue. The nuclei of these cells (Fig 5) are oval or slightly irregular in outline and situated near the center of the cell. The protoplasm stains faintly, being almost entirely replaced by vacuoles which may be so small that they give the protoplasm a finely granular appearance or so large that they distend the cell. Occasionally these vacuolated cells are unusually large and have several nuclei from two to as many as six, collected near the center of the cell. In tissue containing these large vacuolated cells plasma cells occur scattered in considerable number among them. Sections of the dense yellow tissue (see description of gross appearance) containing masses of the vacuolated cells which have been described, exhibit when stained with Scarlach R or Sudan III, large red areas occupying a considerable proportion of the tissue. Microscopic examination shows that the cells which by usual methods are vacuolated are filled with fat in large or small droplets, in osmic acid preparations these globules are black. Areas in which the fat containing cells occur in great abundance are usually in contact with zones containing recognizable macrophages and surrounding foci of suppuration. Transitions from macrophage to vacuolated cells are readily found. The latter appear to be macrophages which have persisted in the meshes of the newly formed fibrous tissue and have undergone advanced fatty degeneration.

In some spots botryomycotic granules are in process of destruction and the surrounding suppuration is in process of disappearance or has completely disappeared. The central coccus-like body may be relatively small, the surrounding tissue may contain no nuclei and appear hyaline. If a cavity persists about the mass of microorganisms polynuclear leukocytes are scant and mononuclear cells have increased at their expense. At a later stage both types of cells have in large part disappeared, the surrounding cavity is absent, and the fixed tissue has approached to the immediate neighborhood of the colony. In contact with the mass of coccus like bodies is a tissue composed of a fibrillated ground-work and elongated spindle-shaped cells with oval vesicular nuclei. These cells have the characters of so called epithelioid cells of the tubercle, and in general directed with their long axes pointing to the central mass, form a zone surrounding the colony. In this zone may occur one or more multinucleated giant cells with many nuclei scattered throughout the cell. Outside of this zone is white fibrous tissue in whose meshes are plasma cells in immense number together with a few lymphoid cells. In some instances a focus or nodule similar to that which has just been described contains no mass of microorganisms in its center and closely reproduces the structure of a tubercle. In the center are one or two large giant cells which have the characters of those seen in tubercles. The nuclei are arranged at the margin of the cell and surround an almost homogeneous area. About the giant cells is a narrow zone formed by a fibrillated

ground-work containing a few cells of epitheloid type. This fibrillated stroma may stain deeply with eosin and exhibit a hyaline appearance. Further outward epitheloid cells are mingled with numerous plasma-cells. Giant cells containing micrococci have been found.

Collections of coccus-like bodies forming large lobulated colonies occur in abundance throughout the lesion. This microorganism acting as an irritant has caused a series of changes in the liver. There is destruction and disappearance of tissue in the immediate neighborhood of the colony and accumulation of polynuclear leukocytes, a cavity containing purulent exudate is formed about the microorganisms. White fibrous connective tissue is formed in abundance in the wall of the abscess. At the margin of the abscess cavity mononuclear cells make their appearance, and acting as phagocytes (macrophages), ingest polynuclear leukocytes, red blood corpuscles and other cells and attain a size many times that of a polynuclear leukocyte. The fibrous tissue nearby is at first rich in cells, containing plasma-cells in immense number. The process of phagocytosis of polynuclear leukocytes and other cells at the margin of the abscess cavity represents an early stage in the process of healing and tends to bring about the disappearance of pus about the parasite. As pus is absorbed the surrounding fixed tissue grows into contact with the mass of microorganisms which are now perhaps killed but not yet dissolved. Cells of epitheloid type and giant cells similar to those of the tubercle come into contact with the persisting microorganism. A lesion resembling, but not identical with, the tubercle is formed. The colony of cocci finally disappears. In the newly formed fibrous tissue between the abscesses there are areas in which large vacuolated cells are so abundant that they form a conspicuous element of the tissue. These cells appear to be mononuclear phagocytes (macrophages) which have persisted in the wall of the abscess and undergone fatty degeneration. They are in places so abundant that they give to the tissue a deep yellow color. Large abscess cavities occur at the advancing margin of the lesion whereas its center is formed by dense fibrous tissue.

#### HUMAN BOTRYOMYCOSIS

Botryomycosis in man was first described by Poncet and Dor<sup>10</sup>. On the hand of a woman near the digito-palmar fold of the little finger an indolent red spot ulcerated and gave place to a pedunculated tumor the size of a small nut. In sections of the tumor they found the masses of coccus-like bodies to which Bollinger gave the name *Botryomyces*, and by personal observation convinced themselves of the identity of the bodies they observed with those found in the fungus-like growths from the spermatic cord of geldings. Poncet and Dor have perhaps diminished for subsequent observers, the value of these bodies as criteria for the identification of botryomycosis by the interpretation which they have offered. They have maintained the untenable view, wholly unsupported

by the bacteriologists who have studied botryomycosis, that the peculiar bodies are not microorganisms, but products of the degeneration of tissue cells. They regard the coccus-like bodies as pyknotic nuclei. From the lesion Poncet and Dor isolated a staphylococcus, which inoculated into the udder of an ass, produced a small pedunculated growth. No examination of the nodule was made. Poncet and Dor have described as botryomycosis three small pedunculated growths, two being on the hand and one on the most prominent point of the stump formed by amputation of the arm at the shoulder.

Faber and Ten Siethoff<sup>12</sup> have described a group of little nodules on the border of the eyelid occurring at the site of a styne in a boy who had tended a horse suffering with a fungoid growth from the cut spermatic cord. In the viscid pus squeezed from the lesion were mulberry-like masses with the structure of those which occur in the horse. Pedunculated tumors containing similar bodies have been observed in France by Sabrazes and Laubie<sup>13</sup> (in one case on the auricle, in a second on the palm of the hand), and by Delore and Gauthier<sup>14</sup> (in one case above the eyebrow, in a second on the finger). Similar observations have been made in Switzerland, Reverdin and Gulhard<sup>15</sup> have described a pedunculated tumor the size of a pea on the palm of the hand, and Galli-Valerio<sup>9</sup> has seen a nodule of similar size and shape on the anterior surface of the fore-arm.

The disease is apparently much more common in northern Africa than in Europe, and French physicians living in Algeria have described in considerable number instances of a similar but much more severe disease. Brault<sup>10</sup> has described two cases in which small pedunculated tumors containing the characteristically-grouped microorganism have occurred on the fingers of women in Algeria. Legrain<sup>17</sup> has described a considerable number of cases of botryomycosis. Attached to the dorsal surface of the right hand of a Berber woman he found a tumor the size of her fist, it consisted of five masses each pedunculated and the whole attached by a narrow base. A tumor in another Berber woman made its appearance on the stump of a finger accidentally amputated and attained the size of a large mandarin. It was removed, but reappeared, forming a mass larger than before, the growth did not invade the underlying muscles or tendons.

12 Faber and Ten Siethoff. *Nederlandsche oogheelkundige bijdragen* 1897. Quoted by Bodin.

13 Sabrazes and Laubie. *Arch. gèn. de méd.*, November, 1899, *Arch. de parasit.*, 1898, 1, 410.

14 Delore and Gauthier. *Gaz. d. hôp.*, Nov. 8, 1900.

15 Reverdin and Gulhard. *Rev. méd. de la Suisse romande*, 1900, No. 11, p. 500.

16 Brault. *Arch. de parasitol.*, 1901, iv, 308.

17 Legrain. *Arch. de parasitol.*, 1898, 1, 148.

In a subsequent publication, Legrain<sup>18</sup> described other growths on exposed surfaces the largest of which was the size of a child's head. Somewhat similar observations have been made by Archibald<sup>19</sup> on material sent to him from various parts of the Sudan, seven growths removed from the scalp, breast, arm, hand, foot or cheek of natives contained agglomerations of coccus-like microorganisms identical with those peculiar to botryomycosis. The same bodies had been previously observed by a member of the laboratory staff in a growth removed from a camel. In one instance the lesion occurred in a native woman, 45 years of age, who had suffered with a swelling of the breast since childhood, it implicated the entire breast, resembled a fungoid cancer and exuded grayish-white pus from numerous sinuses. In another case a tumor of the scalp implicated the underlying bone and from sinuses on the surface thin pus-containing yellow granules escaped.

Butler and Welsh,<sup>20</sup> in New South Wales, found a swelling outside of the left orbit causing softening of the temporal bone in a child 4 years of age. The scant viscid pus contained numerous yellow granules which consisted of masses of cocci. In a Japanese Kayser and Gryns<sup>21</sup> found the right foot swollen and riddled with sinuses from which escaped exudate containing botryomycotic granules.

#### PSEUDO-BOTRYOMYCOSIS

Poncet and Dor identified with botryomycosis of the horse the pedunculated fleshy growths in which they found the mulberry-like bodies described by Bollinger. Subsequent writers have given the same name to similar pedunculated nodules, even though they have failed to demonstrate the presence of these readily recognizable bodies. Such growths having the structure of redundant granulation tissue have been described as botryomycosis by Bodin<sup>22</sup> (two cases), Spourgitis<sup>23</sup> (two cases), Gehinet<sup>24</sup> (six cases), Alglave<sup>25</sup> (two cases), Thévenot and Alamartine<sup>26</sup> (five cases), Lenormant<sup>27</sup> (five cases), and others. In none of these cases have botryomycotic colonies been found. To the same growths, Kuttner<sup>28</sup> (four cases), who found none of the mulberry-like encapsulated groups of cocci, gave the name *Granuloma telangiectoides*. Two

18 Legrain. Quoted by Gehinet.

19 Archibald. Brit Med Jour, 1910, II, 971.

20 Butler and Welsh. Edinburgh Med Jour, 1910, IV, 115.

21 Kayser and Gryns. Geneesk Tijdschr voor Nederl Indie, 1907, VIII, Ref Bull d l'inst Pasteur, 1908, VI, 863.

22 Bodin. Ann de derm et de Syph, 1902, III, 289.

23 Spourgitis. Paris Thesis, 1900. Quoted by Gehinet.

24 Gehinet. Paris Thesis, 1902.

25 Alglave. Bull Soc anat de Paris, 1906, LXXXI, 524-535.

26 Thévenot and Alamartine. Lyon Chirurg, 1909, II, 154.

27. Lenormant. Ann de derm et de syph 1910, XI, 193.

28 Kuttner. Beitr z klin Chir, 1905, XLVII, 1, Bennecke, München med Wehnschr, 1906, 1553.

German writers, Reitmann<sup>29</sup> (one case) and Kreibich<sup>30</sup> (three cases), have adopted the same name for similar growths. Jacquet and Barré,<sup>31</sup> who, like the writers just named, found in their tumors no structures having the characters of so-called botryomyces, think that the use of the name botryomycosis should be discontinued, and the growth they describe should be designated benign hypertrophic granuloma or pseudo-botryomycosis.

Hartzell,<sup>32</sup> describing the same lesion observed in this country (Philadelphia), has suggested *granuloma pyogenicum* to replace botryomycosis of French authors, and this name has been adopted by Sutton,<sup>33</sup> who has described a case which occurred in Liberty, Mo. Wile<sup>34</sup> has described as granuloma pyogenicum two instances of small pedunculated nodules observed in New York City, one on the cheek of a child 8 years of age, the other hanging from the navel of an infant 2 months old. The nodules had the histological structure of granulation tissue, in the first instance richly supplied with blood-vessels. No masses of encapsulated cocci were found within the nodules, but scattered cocci were found at the periphery. Wile describes as typical instances of the same lesion the cases of Hartzell, Kuttner, Reitmann, Kreibich and Jacquet and Barré, in none of which were found the characteristic botryomyces of Bollinger, and reaches the conclusion that botryomycosis does not occur in man, he doubts, indeed, the occurrence of a disease, botryomycosis, in the horse, but does not discuss the subject at length.

It is apparent that the diagnosis of botryomycosis has repeatedly been made from the clinical characters of the lesion. A growth makes its appearance usually at the site of an injury on an exposed skin surface, in most instances on the hands or face, and grows rapidly, attaining the size of a small pea or nut. With excessive growth in all directions the mass assumes a mushroom-like or pedunculated form. It is reddish and fleshy in appearance, superficial ulceration occurs frequently and bleeding is readily induced. After partial removal rapid growth occurs. Histological examination shows the usual structure of granulation tissue, young connective tissue is infiltrated with leukocytes and mononuclear cells, and in some instances with plasma cells. In some instances dilated blood-vessels are abundant, but in other instances blood-vessels are not more conspicuous than those in granulation tissue. It is undoubtedly inappropriate to designate this lesion botryomycosis solely because it is fleshy in appearance and pedunculated. In the absence of demon-

29 Reitmann Arch f Derm u Syph, 1908, xci, 185

30 Kreibich Arch f Derm u Syph, 1909, xciv, 121

31 Jacquet and Barré Ann de derm et de syph, 1909, v, 574

32 Hartzell Jour Cutan Dis, 1904, xxxi, 520

33 Sutton Am Jour Med Sc, 1911, cxlii, 69

34 Wile Jour Cutan Dis, 1910, xxviii, 663

stration of the yellow granules which are peculiar to botryomycosis, the diagnosis is no more possible than the diagnosis of actinomycosis in the absence of the ray fungus. Schridde<sup>35</sup> has recently described protozoa-like bodies within large mononuclear phagocytes found in a pedunculated growth similar to those which have been described. These intracellular bodies are round, oval, semilunar or pear-shape and present some resemblance to the bodies found with kala-azar and oriental sore. No botryomycotic granules were noted in the nodule in which these bodies were found, and he regards the growth as an example of the lesion to which Kuttner gave the name *granuloma telangiectoides*.

#### BOTRYOMYCOSIS OF HORSES IN THE UNITED STATES

I have been able to obtain no literature on the occurrence and distribution of botryomycosis of horses in the United States. Through the kindness of several veterinary physicians I have received information concerning its occurrence. Dr V A Moore, at the New York State Veterinary College, Ithaca, New York, has seen no instance of the disease. Dr J R Mohler, Chief of the Division of Pathology, United States Bureau of Animal Industry, Washington, has written me as follows. In looking through our card-index catalogue we have failed to find any references to literature on the subject of the occurrence of this disease in this country. Our records of pathological specimens show that Dr Leon A Reek of Melbourne, Fla., submitted some tissues from a horse on Nov 4, 1909, Record No 3,418, which showed the presence of botryomycosis. This disease in all probability exists in this country, but the cases are not reported.

Dr Maximilian Herzog has seen several cases in the hospital of the Chicago Veterinary College, but believes that the disease is infrequent in Illinois. Dr A T Kinsley of the Kansas City Veterinary College, writes as follows.

I have found three cases in horses in Kansas City, two of them involving the spermatic cord, as the sequel of castration. The other involved the point of the shoulder and apparently resulted from infection from a bruise caused by the collar. I have had specimens sent to our laboratory from North and South Dakota, two cases from Nebraska, several from Kansas and one from Iowa in the last five years. In my opinion these cases are not at all rare although I do not know that they are diagnosed commonly, usually being passed over as cases of infection without specific diagnosis.

During four years in Colorado, Dr B F Kaupp saw one instance of botryomycosis, the disease occurring in a mule.

The foregoing data indicate that botryomycosis in horses is uncommon in the states of the Atlantic coast, whereas in the central portion of the United States it is more common. A considerable number of instances have been observed in Kansas City, Mo., a part being from Missouri, a part from neighboring states.

35 Schridde *Deutsch med Wehnschr* 1912 *xxxviii*, 218

The unusual nature of the lesion which has been described suggests some unusual mode of infection. Botryomycosis of the human skin is not uncommon in certain tropical countries, yet no record has been found of botryomycosis of an internal organ. In the present case the lesion appears to have been primary in the liver and its occurrence here suggests that infection may have occurred by way of the gastro-intestinal tract. There is no evidence in favor of this view save the statement that one cow from which the child received milk at the time of her infection was affected with a fatal wasting disease. Botryomycosis of cattle has been observed, but is uncommon; the disease occasionally attacks the udder.

#### SUMMARY

Bacteriological examinations indicate that the disease of horses, cattle and swine known as botryomycosis is caused by a microorganism resembling *Staphylococcus pyogenes aureus*, but characterized by the formation of compact colonies held together by a homogeneous material which forms a kind of capsule. About these colonies or granules which are formed only in the tissues there is suppuration and tissue formation producing a lesion which has all the characters of the infectious granulomata.

Human botryomycosis has been observed most frequently in tropical or subtropical countries such as Algeria, the Sudan, Australia and Java. It has been observed in France and Switzerland, but heretofore has not been observed in the United States.

The disease in man affects exposed surfaces such as the hands or face, and has repeatedly followed injuries of infected parts. Pedunculated masses of considerable size may be formed. They consist of newly-formed fibrous tissue in which are foci of suppuration and sinuses opening on the surface. The peculiar botryomycotic granules are always present.

Small pedunculated growths having the structure of exuberant granulation tissue have frequently been described as botryomycosis, although the microorganism peculiar to the disease has not been discovered in the lesion. There is no demonstrable relation between these growths, which have been designated granuloma pyogenicum, telangiectatic granuloma or pseudo-botryomycosis, and botryomycosis as it occurs in man and lower animals.

The case which has been described represents, as far as I have been able to determine, the first instance of the disease described in this country, and is, it seems, the first instance in which it has affected an internal organ. The disease has attacked a child 11 years of age. A massive lesion replaces almost the entire liver and consists of fibrous tissue and foci of suppuration within which occur botryomycotic granules.

in large number It is not improbable that some peculiar mode of infection explains the unusual situation of the lesion The child received milk from several cows, one of which died with a wasting disease, but no more definite history can be obtained Botryomycosis has been observed in domestic animals in Missouri where the human instance of the disease occurred

For the photographs I am indebted to the kindness of Dr R H McBaine  
The drawings have been made by Mr C D Jarrett  
1806 Locust Street



# A CASE OF FOREIGN BODY IN THE HEART

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Numerous cases have been reported in which foreign bodies have been found in the heart at autopsy. In the vast majority of instances entrance to the heart was gained directly through the chest wall. The following case is of especial interest, therefore, as one in which the foreign body reached the heart by way of the venous system, access to the latter having been gained from the digestive tract.

## CASE REPORT

*History*—D H, male aged 49, entered St Luke's Hospital, in the service of Dr Austin W Hollis, May 17, 1912, complaining of nausea, fever and muscular pain. Two weeks before entrance, following a spree of five days' duration, the patient had been seized with nausea and vomiting, everything taken by mouth being immediately expelled. The vomitus consisted of food just taken, and the patient had never noticed that it contained either blood or bile. His condition remained much the same for five days, when he began to suffer from fever and pain in the back and legs. He had no headache, nose bleed or diarrhea. Abdominal pain, urinary disturbance, dyspnea and cough were also absent.

*Examination*—On entrance to the hospital, the temperature was 103.6 F, respiration 24 and pulse 100, regular and of good force. Blood-pressure was 140. There was no dyspnea, cyanosis, jaundice, edema or rash. The pupils were equal and regular, and reacted normally. The ears, nose, mouth and throat were negative. The lymph nodes were not enlarged. There was no rigidity of the neck. Knee jerks were present and not exaggerated. There was marked tremor of the fingers. The heart apex impulse was neither visible nor palpable. The left border was 11.5 cm from the midsternal line, the right border was beneath the sternum. The heart sounds were distant but of good quality. There was a short systolic murmur at the apex which was not transmitted. There were no accentuations. Examination of the lungs was negative. The abdomen was somewhat distended and there was slight general tenderness. The liver edge was felt one inch below the free border of the ribs and the edge of spleen could be felt just beneath the costal margin.

A blood culture taken May 18 showed numerous colonies of *Streptococcus viridans* and *Bacillus coli communis*.

On May 18 the white blood-cell count was 22,000, polymorphonuclears 86 per cent, lymphocytes 14 per cent. The Widal reaction was negative. The urine was clear, acid, specific gravity 1.015 and showed a faint trace of albumin. The sediment contained many polymorphonuclear leukocytes and no casts. The stools were not examined for blood, but were never tarry.

On May 20 there were many moist râles and a small area of bronchovesicular respiration and moderate dullness over the right base. The white blood-cell count had risen to 34,000, polymorphonuclears 84 per cent, lymphocytes 16 per cent. The

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\* From the Pathological Department of St Luke's Hospital, New York, F C Wood, M D, Director.

patient ran a markedly irregular temperature varying from 102 to 108 F. He grew gradually worse and died May 21.

*Necropsy*—Autopsy was performed six hours post mortem. The body showed no marks of external violence, no edema or jaundice, and no ecchymoses of the conjunctiva or elsewhere. The peritoneum was normal and contained no fluid. The dome of the diaphragm was on a level with the fifth rib on either side. The liver edge was at the costal margin. There were 300 cc of slightly cloudy yellow fluid in each pleural sac. The apices of both lungs were bound by old fibrous adhesions and there were small scattered areas of bronchopneumonia in the right lower and left upper lobes. The pericardium contained 75 cc of unclotted blood. Protruding 1.5 cm from the posterior tip of the right auricle was the end of an ordinary wooden toothpick which measured 6.8 cm in length. The other end could be felt within the auricle, pressing against its anterior wall at the right auricular appendage. Over this end the wall was thinned, white and covered with fibrin over a small area about 3 mm in diameter. The toothpick was held in place within the auricle by a soft "chicken fat" clot. At the upper part of the pericardium posteriorly there was an area, 1 cm in diameter, which was abraded, but not pierced, by contact with the end of the toothpick. Adherent to the surface of the pericardium were several small plaques and shreds of fibrin. Numerous small ecchymoses, from pin-point to 1 mm in size, were present on the epicardium, especially numerous over the upper posterior part of the left ventricle. The heart was preserved in gross without sectioning.

The pharynx, larynx, trachea, esophagus and stomach were all normal. On the posterior wall of the duodenum, 14 cm beyond the pylorus, at the lower part of the descending portion where it lay directly over the inferior vena cava, was a small ulcerated area, about 5 mm in diameter. Extending backward and upward from the base of this ulceration was a sinus, 1.5 cm in length, which easily admitted a probe 2 mm in diameter, leading directly into the inferior vena cava. The intestine was otherwise normal. The intestinal contents were of normal brown color.

In the anterior wall of the inferior vena cava, 8 cm below the entrance of the hepatic vein was the opening of the sinus from the duodenum previously described. Surrounding this opening the wall over an area 5.5 cm lengthwise of the vessel and 2.5 cm transversely, showed a rough, eroded surface covered with a small amount of loose fibrin of a greenish color, suggesting bile staining. A small fibrinous clot adherent to the edge of the sinus had evidently plugged it before death.

The other organs, except for a large soft spleen weighing 360 gm, showed nothing of particular interest either grossly or on microscopic examination.

#### OTHER REPORTED CASES

Nineteen cases have been reported in the literature in which foreign bodies have been found in the heart at autopsy, omitting the large number in which entrance to the heart was gained directly through the chest wall. The articles found were needles, pins, fish-bones, teeth, a thorn, etc. In one of these nineteen cases a needle had pierced the bronchus, pericardium and heart. In a second case the patient had swallowed two false teeth on a gold plate. The gold plate had pierced the esophagus and pericardium, the patient dying of a purulent pericarditis. In a third case, a fish-bone had pierced the stomach wall, near the esophageal opening, and subsequently the diaphragm, pericardium and heart, the sharp

end of the bone having been found protruding into the heart and the blunt end into the stomach. In two cases there was a definite history of swallowing the foreign body which was found in the heart, but no lesion of the digestive tract and no indication of the route followed were found. These two cases are of interest on account of the length of time during which the foreign bodies had in all probability been present in the heart and the slight or entire lack of heart symptoms due to their presence. In one, a case reported by Ambrose, a pin, which had been swallowed nine years previously, was found in the wall of the right ventricle. The patient died of perforated gastric ulcer without having had heart symptoms in the interval. In the second case, reported by Kussmaul, a thorn of *Prunus spinosa*, covered by a thick layer of fibrin, was found free in the cavity of the right ventricle. The spine had been swallowed one and a half years previously, and following this the patient had been troubled for some time with precordial pain. He died of pulmonary tuberculosis.

In the remaining fourteen cases no indication of the place of entrance was found and no definite history was obtained. In twelve of these the foreign body was believed to have been swallowed, and may have been in all. In several, however, it was a question whether the foreign body might not have been inserted through the skin. In four of the cases, the writers believed, but without proof, that entrance to the heart was obtained directly through the esophagus and mediastinal tissues.

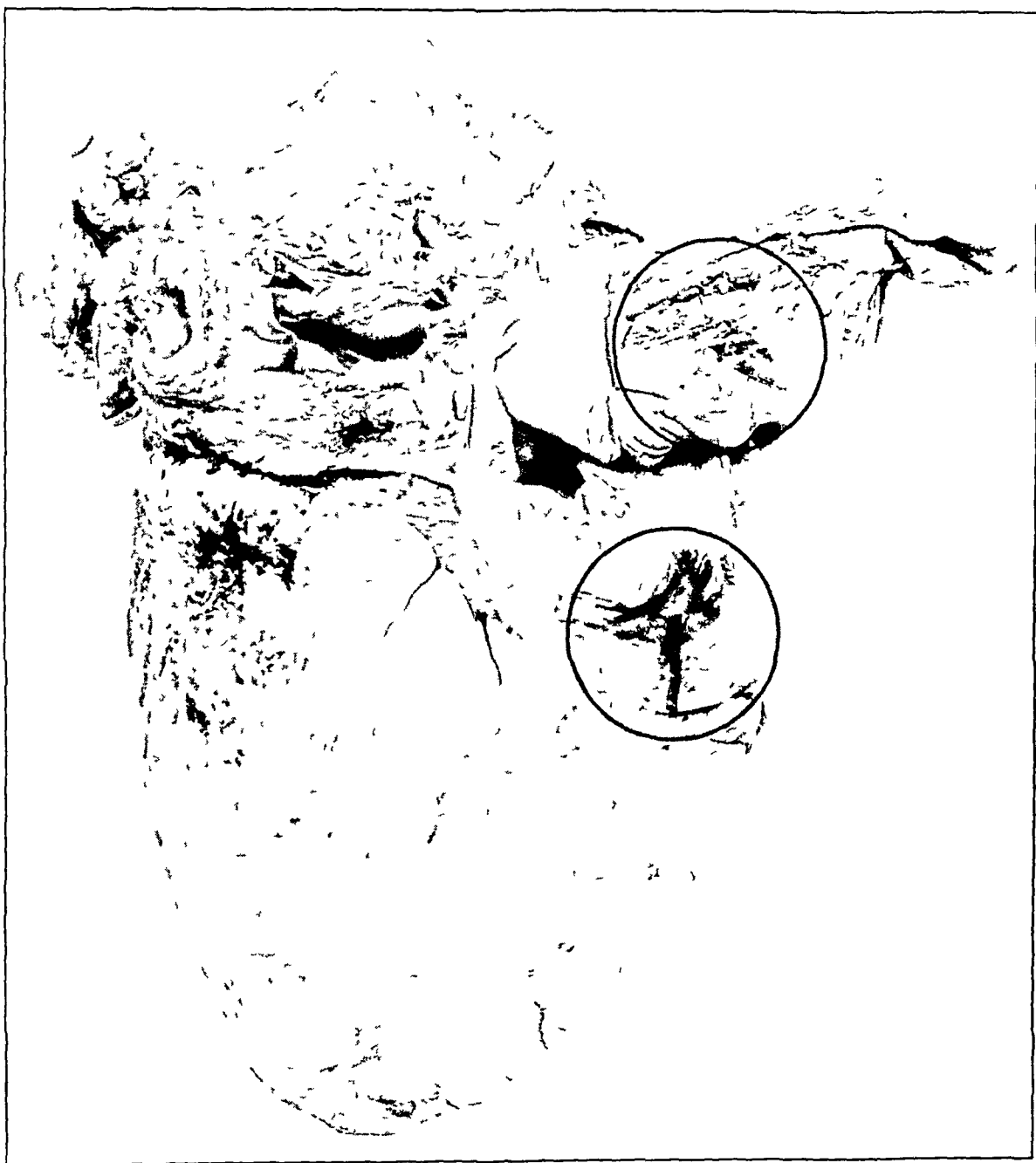
A case reported by Benda, not included in the above series, is also of interest. In this a fish-bone was found in the superior mesenteric vein, but no lesion of the digestive tract was discovered.

#### DISCUSSION

The case here reported seems then to be unique in that the foreign body was proved to have reached the heart by way of the blood-stream, its point of entrance into the latter from the intestine having been demonstrated. It is probable that this occurred in some of the cases quoted above, and its possibility is discussed at considerable length in the literature. Oppel, working with rabbits, was unable to demonstrate that needles could travel in the blood-stream, and doubts whether this ever occurs in man. Haecker, from experiments on dogs, arrived at a similar conclusion.

The route traveled by the toothpick in the case reported was a short one. A smaller object, however, which could easily have passed the tricuspid and pulmonary orifices, would have been carried on to the lungs, and one small enough to pass easily through vessels of small caliber might have traveled a much greater distance to the heart. A wooden object

would naturally be more easily carried along by the blood-stream than a metal one, especially if the latter were sharp-pointed, as a needle or pin. There seems however little room for doubt that many of the foreign



The lower circle surrounds the end of the toothpick which protrudes from the posterior tip of the right auricle. The upper circle surrounds the surface of the pericardium at the point where it has been roughened by contact with the protruding end of the toothpick.

bodies, as fish-bones and even pins and needles, which have been found in the heart reached it by way of the blood-stream as did the toothpick in this case.

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includes the late or tardy epilepsies. This condition having no bearing on our findings, will not be discussed. It is, however, fitting to call attention to the so-called epileptic convulsions accompanied by stoppage of the heart, bradycardia or other arrhythmia.

Bradycardia has been noted by Seguin (21-21) Corkey and Hubberty (11-76), Drummond (5-15), Gibbings (12) and many others. In the light of our present knowledge of heart-block it is extremely probable that it was this condition which the above authorities observed.

Stoppage of the heart (?) has been observed by Moxon and Tagge and Smith while auscultating the heart. Failure of the pulse has been observed by Hughlings Jackson and Russel. Whether these cases were heart-block or hemisystole cannot be said, for lack of graphic records. Munson<sup>1</sup> did not find a single case of stoppage of the heart in epilepsy, employing graphic methods as a means of study.

There are found in the literature numerous references to the abnormal condition of the heart in epilepsy. Valvular lesions, hypertrophy and arrhythmias have been frequently noted.

Browning,<sup>2</sup> after examining 150 cases, states that normal sounds and a normally acting heart are the exception rather than the rule.

Of the forty-four cases examined by us, thirty-five showed an abnormal condition of the heart, of these, ten showed gross lesions and twenty-five a functional change manifested by hemic murmurs, abnormality of sound and sinus arrhythmia. Valvular lesions were observed four times. Hypertrophy was observed seven times. Diastolic irregularity was observed twelve times. Abnormal sounds were observed thirteen times. Hemic murmurs were observed four times. Heart block was observed once. Irritable heart was observed once. Nodal rhythm was observed once. Auricular extrasystoles were observed once. The case of heart-block exhibited true epilepsy and not the syncopal attacks of the Stokes-Adams syndrome. Although it is generally agreed that sinus arrhythmia is of vagal origin, no relation between it and the Traube-Hering waves (to be described later) was observed. Hypertrophy of the heart occurred in patients in middle life or above, with two exceptions.

#### BLOOD-PRESSURE

Owing to the diversity of methods employed by the numerous investigators, and the mechanical defects of many of their instruments the work of the older authors, such as Feré, must be discounted. Of the more recent investigations it may likewise be said that the methods differ that the observations have been too limited in number, and that graphic methods allowing of the study of continuous blood-pressure

<sup>1</sup> Munson Jour Am Med Assn, 1908, 1, 681

<sup>2</sup> Browning, Wm Jour Nerv and Ment Dis, 1893, LVIII

curves have not been utilized. It is apparent that one cannot detect a change in blood-pressure occurring within the space of several seconds by the use of such instruments as the Riva-Rocci, Janeway, Stanton, etc.

Summed up, the results of the more recent investigations are as follows. There is a high blood-pressure during the convulsion, the blood-pressure falls rapidly after the convulsion, but remains higher than normal between convulsions. (Plaskuda, Morgenthau, Fleury, L'Allemand and Rodiet and others.)

Our results will be tabulated under the following headings: 1 General blood-pressure. 2 Respiratory change in blood-pressure. 3 Traube-Hering waves. 4 Changes relative to the convulsion.

1 Of 41 cases examined as to general blood-pressure, 18 had a systolic blood-pressure of 120 or below, and 23 above 125 ranging to 200. Of 17 cases examined on the day of a convulsion, seven had a systolic blood-pressure above 135, and 10 were below 120.

The pulse-pressure, estimated by the difference between the systolic and diastolic pressures, was 50 or above in 21 cases, 40 or above in 15 cases and 45 in 5 cases. Of 8 cases showing a pulse-pressure above 55, 5 were either measured on the day of a convulsion or had some cardiovascular disease.

Owing to the paucity of material, and taking into consideration the individual variations, variations of emotion, sensory stimuli, etc., no hard and fast conclusions can be made from this particular part of the work. The systolic blood-pressure and pulse-pressure were higher than normal in a little more than one-half the cases, the pulse-pressure was below normal in many. The cases showing cardiovascular disease had high pulse-pressure. The cases showing high systolic blood-pressure on the day of a convulsion likewise showed a high pulse-pressure.

2 Respiratory change in blood-pressure. In 21 cases showing respiratory changes in blood-pressure our results bear out Erlanger and Festerling's<sup>3</sup> findings. The arterial pressure falls during inspiration and rises during expiration. During the labored breathing following a convulsion, the respiratory changes in blood-pressure are very marked.

3 Traube-Hering waves. Under certain unusual conditions, there are found in addition to the respiratory rhythmical falls and rises of blood-pressure, changes in blood-pressure, the waves of which are much larger than those due to respiratory movements. These waves were first described by Traube<sup>4</sup>. Hering<sup>5</sup> considered them as arising as a result of irradiation from the respiratory center. Horatio Wood Jr.,<sup>6</sup> in a

<sup>3</sup> Erlanger, Joseph, and Festerling E G. Jour Exper Med 1912, vol No 4 p 37

<sup>4</sup> Traube. Centralblatt Med Wissensch 1865 p 1881

<sup>5</sup> Hering. Quoted by Horatio Wood Jr (see note 6)

<sup>6</sup> Wood Horatio Jr. Am Jour Physiol, 1899 No 2 p 352



study on the origin of Traube waves, comes to the conclusion that they do not arise in the respiratory center. He was able to paralyze the respiratory center through the action of veratrin, the vasomotor center remaining intact. Under these conditions he was still able to observe Traube waves (Fig 1).

The ultimate cause of these waves is not well understood but they are probably due to a rhythmical activity of the vasomotor center. Although a rhythmical activity of the vasoconstrictor center is said to be present throughout life there are no definite data relative to the occurrence of these waves in man.

They have often been observed during experiments on animals especially in experiments increasing the intracranial tension. They have likewise, occasionally been observed in apparently normal human subjects. However, although present at times, they are the exception rather

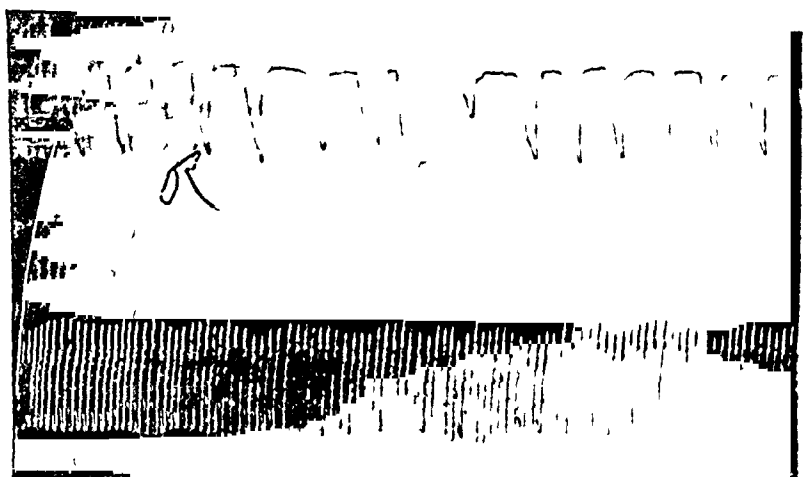


Fig 1—Traube-Hering waves not due to respiratory change. Upper tracing respiration, lower, blood pressure.

than the rule. Many other waves of change in blood-pressure may be observed in man and should be definitely differentiated from the Traube-Hering waves. Emotion, muscular movement, peripheral stimulation etc., all produce change in the continuous blood-pressure tracings. Changes due to muscular movements can easily be differentiated, as pointed out by Erlanger,<sup>3</sup> those due to emotion, etc., are not rhythmical and do not have a gradually increasing and diminishing size. In the interpretations of our tracings the following conditions were insisted on before Traube-Hering waves were said to be present: 1. The column of mercury in the manometer had sunk to its lowest level after inflating the arm-band before the drum was started. 2. All muscular movements were carefully watched for, and marked as such on the drum. 3. All waves due to emotion and other causes were excluded. 4. Following the convulsion the column of mercury was at the same level as before it. The

waves will be described relative to their occurrence, length and relation to pulse change

Of the 44 cases, 24 showed the presence of Traube-Hering waves. Of 15 cases examined on the same day as the convulsion, 7 showed marked waves, 6 moderate waves and 2 no waves.

Of 14 cases examined within five days after a convulsion, 3 showed marked waves, in 7 waves were present and 4 showed no waves.

Of 15 cases examined more than five days after, one showed moderate waves twenty days from a convulsion. It was observed in those examined immediately preceding and following a convulsion that the waves were more marked at this time.

Of the 24 cases showing waves, 13 were present in cases showing a definite aura, 4 in those showing no aura and 7 in whom a history could

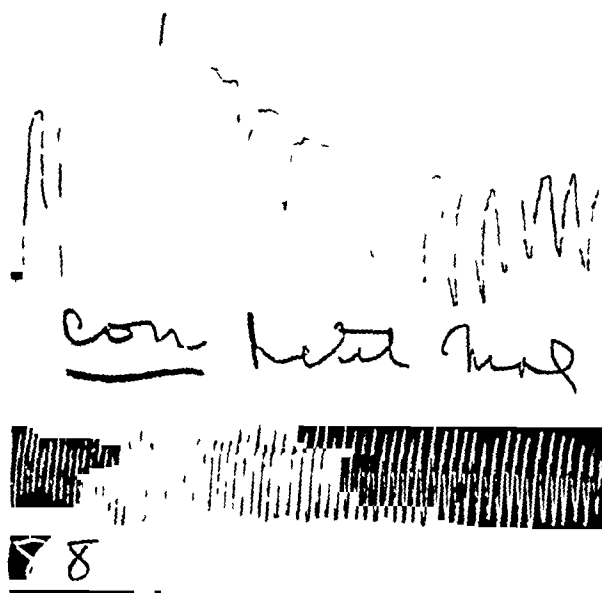


Fig. 2—Relatively low blood-pressure during petit mal attack

not be obtained. Four other cases showing an aura had no waves. The tracings on these cases were not taken on the day of a convulsion and none of them had a pneumogastric aura.

The duration of the waves ranged from  $13\frac{1}{3}$  to 35 seconds. The greater number ranged from  $13\frac{1}{3}$  to 26 seconds. The duration of the waves remained constant in each individual, and the series may be divided into three groups possessing waves 13.33 to 18.66, 20 to 22 and 24 to 28 seconds.

Of 39 cases the pulse-rate was slower during the high blood-pressure in 17 cases, more rapid in 3 and unchanged in 18. It is safe to say that when the pulse changes in rate it is usually slower during the period of high blood-pressure.

4. Pulse and blood-pressure in relation to the convulsion. It would be useless to give a review of the literature on these points for the reason-

outlined above. Most authors agree that there is an increase of blood-pressure preceding and during the convulsion, that it rapidly falls after the convulsion, but remains higher than normal throughout. The pulse-rate is said by most observers to be increased during the convulsion. Some state that it is slow, it is possible that these cases may be the bradycardias of heart block. Moiranthaler goes further and states that the blood-pressure is labile after the convulsion.

We have obtained tracings showing continuous pulse- and blood-pressure curves before, during and after the convulsions, on three dif-

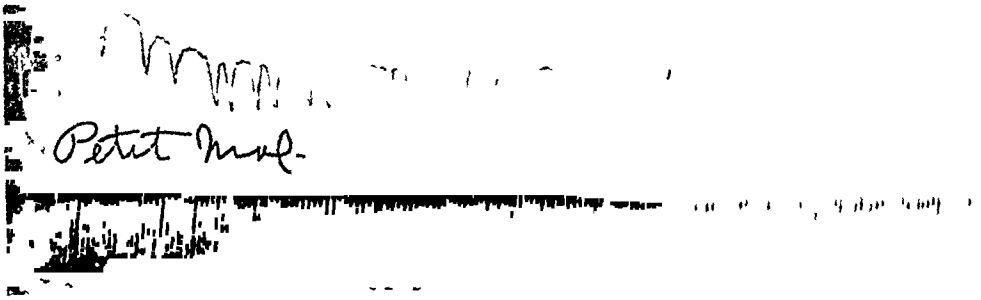


Fig 3—Alternating type of respiration following a petit mal attack

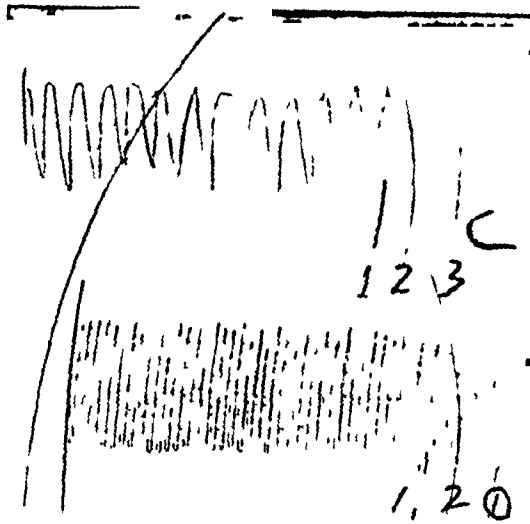


Fig 4—Petit mal attack 1 Drop in blood-pressure 2 Apnea 3 Convulsion

ferent patients, and on one during and after the convulsion. In one case we have obtained eight tracings, showing seven petit mal and one grand mal attack each. In another case two grand mal attacks and in two cases one grand mal attack each. In all of these cases there was seen in addition to the Traube-Hering waves, (1) a preliminary rise in blood-pressure occurring from twenty-six to sixty seconds before the convulsion. Where the rise occurred over thirty seconds before a convulsion the blood-pressure usually fell again slightly, (2) immediately preceding the con-

vulsion by from nine to twelve seconds and in one case twenty-eight seconds (this was a case of grand mal attack) there was a sudden marked drop in blood-pressure lasting from eight to thirteen seconds (Fig 2) The pulse in every instance became rapid and remained so during the convulsion and for a short time following it The increase in rapidity of the pulse occurred at the time of drop in blood-pressure The blood-pressure remained relatively low during the time occupied by the petit mal attacks in all fits, and rose within five seconds after the attack The blood-pressure rose rapidly and markedly, in many instances showing rhythmical variations, and then gradually subsided to the normal level

In the grand mal attacks we are unable to state positively whether the relatively low blood-pressure persists throughout the entire attack, because of the interference by arm movements and the consequent late appearance of a regular blood-pressure curve In one of these tracings it can plainly be seen that the blood-pressure is low for a considerable time during the convulsion It must be said, however, that in tracings taken during the grand mal attacks the blood-pressure is high at cessation of the attack In one attack of petit mal type in which we were able to note the beginning of the aura, it was found to follow the drop in blood-pressure by two and two-thirds seconds and to precede the apnea by two seconds

#### RESPIRATION

The respiration will be studied from two standpoints 1 Rhythmical change in type of respiration 2 The respiration in relation to the convulsion

In twelve of the forty-four cases of rhythmical change from rapid, regular and shallow, to slow, irregular and deep was noted within a short period preceding and following a convulsion Eleven of these cases showed well-marked Traube-Hering waves of blood-pressure The changes in respiration did not have any definite relation to the changes in blood-pressure indicated by the Traube-Hering waves, nor to the blood-pressure in general A change similar to this has been noted in meningitis by Conner<sup>7</sup> (Fig 3)

In five cases one or more periods of apnea were observed lasting from sixteen to thirty seconds During this period there was seen a fall in blood-pressure and in one case two rhythmical waves of change in blood-pressure This apnea occurred at times having no bearing on the convulsion

A study of the respiratory change in relation to the convulsion was possible in five tracings taken during petit mal and three tracings during grand mal fits in three different patients In every example of petit mal attacks in one patient it was seen that there was a cessation of respiration preceding the convulsion by four to twenty-six seconds, more often four

to nine seconds. The apnea persisted throughout the convulsion and lasted from thirteen to sixty seconds. It was interrupted in a few instances by several deep and irregular respirations. The apnea commenced at the height of inspiration. It was in every instance preceded by the fall in blood-pressure by from two and two-thirds to six and two-thirds seconds.

In the tracings of the three grand mal attacks in each instance the fall in blood-pressure preceded the apnea and the apnea preceded the convulsion as in the case with petit mal attacks. We are unable to state definitely how long the period of apnea lasted relative to the convulsion in these cases. The tracings show either an apnea or an apnea interrupted by slow and irregular respiratory movements.

Before taking up the discussion of the relation of our findings to the various theories of the pathogenesis of epilepsy we shall make a résumé of those conditions which may have a bearing on a causal relation to epilepsy.

There were present a number of diastolic arrhythmias considered to be of vagal origin. A large number of cases showed Traube-Hering waves, especially those cases having an aura. These waves were particularly prominent during the time near or following a convulsion, and practically disappeared after five days.

Rhythmical respiratory movements were found in a considerable number of cases, with one exception always associated with, but having no relation to, the Traube-Hering waves.

The convulsions showed a sequence of events as follows. A preliminary rise in blood-pressure followed by a sudden fall, then an aura, then a period of apnea and then the convulsion. The blood-pressure remains relatively low throughout the petit mal and also probably throughout the grand mal attacks. The pulse becomes rapid with the fall in blood-pressure and remains so during the convulsion (Fig. 4).

The literature on the pathogenesis of epilepsy is especially rich. The theories are numerous and contradictory and the evidence is inconclusive. We shall content ourselves with mentioning some of the theories, first as to the stimulus that determines the discharge, and second, as to the seat of discharge.

Relative to the nature of the stimulus we shall confine ourselves to the question of anemia and hyperemia of the brain. Anemia of the brain as the cause of unconsciousness and convulsion has been supported by Kussmaul and Tenney, Nothnagel, Riegel and Jolly, Gutnikow and many others. The gap between the several steps of reasoning employed by these authors is considerable.

The facts that anemia of the brain can produce convulsions and that

a pallor of the face has been observed by these authors during the attack, is certainly insufficient evidence to establish anemia as the cause of unconsciousness or convulsions

On the other hand, hyperemia of the brain has likewise been supported by many, Landois, etc. Recently it has been found that, during experimentally produced epilepsy, hyperemia and not anemia of the brain is present during the convulsion (Rabinowitch, Berger). We shall refer to these observations again.

As to the seat of discharge, we have a great number of observers arrayed against one another, one group assuming the medulla and pons to be the site of discharge, Nothnagel, Van d'Kolk, Reynolds, Echeverria, Kussmaul, etc., the other placing it in the cerebral cortex—Charcot, Ferrier, Luciani, Gowers, etc.—while Hughlings Jackson suggests that fits might result from discharge of lesions in either of these two.

It is not necessary to enter into a detailed account of the experimental work tending to prove either of these theories. Suffice it to say that convulsions may be caused experimentally through irritation of either of these regions.

The experimental production of convulsions by irritation of the cortex and the occurrence of convulsions as the result of disease of the cortex has led to the conclusion, as yet unproven, that the greatest number of convulsions originate in the cortex. This does not exclude the medulla and pons as the site of discharge in some convulsions.

J. Hughlings Jackson and H. Douglas Singer<sup>8</sup> suggest that in addition to the cortical type of epileptic fits, there occur, in the human subject, bulbo-pontine (lowest level) fits, analogous to those experimentally produced in some lower animals. They offer in support of this hypothesis a case showing fits which definitely began by convulsions of the respiratory muscles. Of special interest is the observation that with the beginning of the earliest motion of the convulsion, respiration ceased and was not resumed until the end of the fit, which lasted from forty to sixty seconds.

Harvey Cushing<sup>9</sup> has contributed some very important data as to the relation between increased intracranial tension, cerebral anemia and respiration. He has found that at a stage during the height of compression there occur Traube-Hering waves, and Cheyne-Stokes respiration associated with rhythmical change in blood-pressure, the low blood-pressure corresponding to the period of apnea. It would seem that the period of apnea is the result of cerebral anemia produced by the increased intracranial tension and the relatively lower general blood-pressure.

<sup>8</sup> Jackson, J. Hughlings, and Singer, H. Douglas. *Brain*, 1902, **xxv**, 122.

<sup>9</sup> Cushing, Harvey. *Am Jour Med Sc*, 1902, **cxlii**, 375, 1903 **cxlii**, 1017, *Bull Johns Hopkins Hosp*, 1901, **xii**, 290.

It can readily be seen that all experiments on the cerebral circulation must take into consideration intracranial tension, and such experiments as include the opening of the cranial cavity without subsequently closing it, must be discarded.

The fact that increased cerebrospinal pressure has been observed during the convulsion of epilepsy (Bianchi,<sup>10</sup> D'Oimea), adds considerable speculative interest to our observations that there is present an undulatory respiration and Traube-Hering waves together with a fall in general blood-pressure preceding the convulsion in all our cases.

It would be important to determine by further work any possible relation between the changes found by us and any change in the cerebrospinal pressure, perhaps similar to the changes found by Cushing in experimentally producing increased cerebrospinal pressure. From our experiments no definite conclusions can be made as to the state of the cerebral circulation at the time of convulsion, inasmuch as the intracranial tension was not measured. A vasoconstriction of the peripheral vessels does not necessarily indicate a similar condition of the cerebral vessels.

Our one case in which petit mal attacks were studied is very similar to the case described by J. Hughlings Jackson and H. Douglas Singer and shows definitely that, whatever the nature of the stimulus, the site of discharge either acts on both the cerebrum and medulla and pons, or on the medulla and pons alone.

The presence of unrest of the vasoconstrictor and respiratory centers shown by the Traube-Hering waves and undulatory respiration, the fall in blood-pressure preceding the convulsion, and the cessation of respiration probably due to vagal interference, as well as the aura of pneumogastric type following shortly after the fall in blood-pressure, all point to the bulbopontine region as a site of disturbance.

The irritation may have commenced at the cortex and spread downward, being felt in the medulla first, or it may have commenced in the medulla and spread upward, in this particular type of case we are of the opinion that the site of discharge is in the medulla. We are unable to say if the same is true of grand mal attacks and obviously cannot make any assertions for epileptic convulsions in general. It is noteworthy that the sequence of events in the petit mal attacks of one patient was the same as that observed in a grand mal attack in the same patient and that two other grand mal attacks in two other individuals presenting a clinical picture of ordinary epileptic convulsions likewise showed similar manifestations.

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<sup>10</sup> Bianchi. *Ann di Neurol*, 1911, *xxix*, Part 3.

## CONCLUSIONS

It may be stated that with regard to the cases observed by us

1 There are present in many cases of epilepsy rhythmical variations of blood-pressure other than those due to respiratory movements

2 The sequence of events relative to a convulsion is as follows A preliminary rise in blood-pressure followed in series by a sudden drop of blood-pressure, a period of apnea, and then the convulsion

3 The blood-pressure was relatively low during convulsions of petit mal type and during some of the corresponding period of the fits of the grand mal type

4 The pulse was rapid during the convulsions

5 A study of the changes in the respiratory and circulatory systems in some of the cases of epilepsy suggests that the site of discharge is in the medulla and pons (the "lowest level of fits" of Hughlings Jackson) Likewise it points to the medulla as participating in the discharge in all cases of epilepsy whether this discharge originates there or not

We wish here to express our gratitude to Dr H Douglas Singer, director of the Institute, for his encouragement and kind assistance



# A MODIFICATION OF RUSSO'S URINARY TYPHOID FEVER TEST, WITH A REPORT OF ITS USE IN ONE THOUSAND CASES, AND A COMPLETE BIBLIOGRAPHY

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As a preface to the discussion of the urinary methylene-blue test for typhoid fever, it seems best to point out a few facts regarding the value of blood-cultures in the diagnosis of typhoid fever. By the use of the more modern methods for the isolation of the typhoid bacilli from the blood, the blood-culture has been so uniformly successful that it is now recognized as the diagnostic means, *par excellence*, especially for an early diagnosis. This procedure is, of course, to be recommended in all cases, but the average practitioner does not possess the necessary laboratory skill or apparatus for this test, the technic being rather difficult. It is for this reason that a number of tests which might be classed as secondary or corroborative are of much clinical value and significance, each one strengthening the physician's diagnostic armamentarium. The urinary methylene-blue test is placed in this class of corroborative tests, and is discussed with that view-point in mind.

## THE RUSSO REACTION

The use of methylene-blue in the urine as an aid in the diagnosis of typhoid fever was first described by Russo<sup>1</sup> in 1905. The technic, as described by Russo, was as follows: To 4 or 5 c c of the patient's urine add 4 drops of a 0.1 per cent aqueous solution of methylene-blue. After thoroughly mixing, examine against the light. A positive reaction is indicated by an emerald or mint green. Any tinge of blue renders the reaction negative. This reaction, according to Russo, is not affected by boiling, nor by the ingestion of such drugs as calomel, quinin, salol and caffeine. If the urine is examined from day to day, a returning bluish tinge denotes the beginning of convalescence, and is regarded by Russo as a favorable prognostic sign. He obtained positive reactions in urines in which the specific gravity was from 1.016 to 1.030. The reaction was constantly negative in normal individuals, both young and old, and in pregnancy, labor, scarlet fever, chicken-pox, small-pox, influenza, acute and chronic bronchitis, lobar pneumonia, bronchopneumonia, acute and

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\* From the Laboratory of Georgetown University Hospital

1 Russo, M. La bleuemetilene-reazione, suo valore clinico. Riforma med., Palermo-Napoli, 1905, xxi, 507

chronic gastric catarrh, gastroenteric fevers, appendicitis, renal calculus, abscess of the liver, articular rheumatism, mitral insufficiency, epilepsy, neurasthenia and malaria. A positive reaction was also present in measles and in some severe cases of tuberculosis. In the latter, the appearance of a positive reaction did not denote the height of the fever, but indicated the severity of the infection. The reaction has no relation to indican and is probably caused by toxins excreted by the kidney. Privisteria later corroborated the work of Russo.

The subsequent work with the urinary methylene-blue reaction has not been particularly extensive, and does not tend to confirm the conclusions of Russo.

Cousin and Costa,<sup>2</sup> using the method as described by Russo, obtained a positive reaction in any urine which was dark, that is, concentrated. This obtained not alone in typhoid fever, but in any other disease in which the urine was dark. By diluting a concentrated urine which had given a positive reaction, a blue or negative reaction was obtained, and by concentrating a pale urine which had shown a negative reaction, a green or positive reaction appeared. They concluded that the production of an emerald or mint green was not a chemical, but a physical phenomenon, in fact, that it was a metachromasia, produced by the yellow of the urine plus the blue of the reagent. They also used the method of Roch, and Boudin and Monchton, by suspending a tube of the blue solution in a large tube of the yellow urine, when a green was produced in the lower portion of the tube. Russo's facts are not disputed, but his interpretations of them are. Their final conclusion is that it is of no diagnostic value, since in any febrile condition the urine is concentrated in the early stages, and gradually becomes lighter in the stage of convalescence. The above conclusions were confirmed by Gandy,<sup>3</sup> Lesieur,<sup>4</sup> Theodoroff,<sup>5</sup> Spieshoff,<sup>6</sup> Frankel, Dmitrenko,<sup>7</sup> Dunger,<sup>8</sup> Dibailoff<sup>9</sup> and Iovanne.<sup>10</sup>

2 Cousin, E, and Costa, S. La Reaction des urines au bleu de methylene dans la fièvre typhoïde. Presse méd., Paris, 1906, xiv, 162.

3 Gandy, C. La Reaction des urines au bleu de methylene dans la fièvre typhoïde. Presse méd., Paris, 1906, xiv, 180.

4 Lesieur, C. Note a propos de la reaction des urines typhiques au bleu de methylene. Bull. soc. med. d. hôp. de Lyons, 1906, v, 256.

5 Theodoroff, H. La Reaction au bleu de methylene de Russo peut elle remplacer la diazoreaction d'Ehrlich? Tausanne, 1907, A. Simmen.

6 Spieshoff, P. Clinical Importance of Russo's Reaction. Novoye v. med., St. Petersburg, 1909, iii, 11.

7 Dmitrenko, F. La Reaction au bleu de methylene en urologie. Semaine méd., 1906, p. 174.

8 Dunger, R. Ueber den Ersatz der Ehrlichschen Diazoreaktion durch die Methylenblauprobe nach Russo. Deutsch. med. Wchnschr., 1906, xxxii, 1582.

9 Dibailoff, S. J. Diagnostic Value of Russo's Reaction. Vrach Gaz., St. Petersburg, 1909, xvi, 5.

10 Iovanne, A. La bleumethylenereazione nelle urine dei bambini sani ed ammalati. Pediatria, Napoli, 1906, iv, 267.

Landolfi<sup>11</sup> agrees with the above authors that the reaction is simply a physical phenomenon. He examined particularly cases of tuberculosis, and whenever the color produced was green or greenish blue, using the method of Russo, he repeated the test after decolorization. The urine was decolorized by first correcting the reaction if alkaline, boiling and filtering to remove the albumin. To 10 c c of the filtrate from 5 to 10 drops of a saturated solution of lead acetate was added, and then filtered through a double filter. With 5 c c of this filtrate the test was made in the usual manner. In a few cases of tuberculosis in the last stage, a positive reaction was still obtained. Working on the basis that a small amount of indican is normally present, a deep green produced with a small amount of indican is considered positive, while a greenish-blue with a large amount of indican is considered negative. He, however, does not regard it as of diagnostic value.

Carletti<sup>12</sup> confirmed the work of Landolfi, and quoted Monchton as believing that the green reaction was due to bilirubin. However, the reaction is present even in urines showing no bile with ammoniated zinc. He stated that the specific gravity and reaction of the urine had no effect, and that the coloration disappeared in from twelve to twenty-four hours, leaving the granules of pigment floating on top although Russo claims that the color lasts about ten days. Carletti considers these as strong arguments in favor of the hypothesis of a physical phenomenon.

Grossi<sup>13</sup> followed the decolorization method of Landolfi and confirmed his results, showing a few positive results even after being decolorized. However, Grossi, claiming that the decolorization was not complete, added a larger quantity of lead acetate and afterwards used animal charcoal to insure a thorough removal of all coloring matter. Using this method, a positive reaction was never obtained in a large series of various diseases in which a positive reaction was obtained before decolorization, in all cases, and in a number when using the method of Landolfi.

The results of the researches of Landolfi, Grossi and Carletti were confirmed by Montefusco,<sup>14</sup> Tolane and Ferrari<sup>15</sup>. The latter also had similar results by decolorization with charcoal alone, as he believed that the other method might cause some chemical changes. An examination of the urine before and after decolorization, showed some slight changes

11 Landolfi, M. La Bleumetilenereazione. Riv. crit. di clin. med. Firenze 1906, vii, 705.

12 Carletti, M. Interno alla così detta bleumetilenereazione. Gazz. d. osp., Milano, 1906, xxvii, 146.

13 Grossi, T. Ancora sulla cosiddetta bleumetilenereazione. Giorn. internaz. d. sc. med. Napoli, n. s., 1907, xlix, 268.

14 Montefusco, A. La bleumetilenereazione nelle malattie infettive. Giorn. internaz. d. sc. med. Napoli, n. s., 1907, xlix, 460.

15 Ferrari, G. Sulla bleumetilenereazione. Gazz. d. osp. Milano, 1907, xxviii, 533.

He also claimed that the reaction was not affected by glucose, indican, creatinin and acetone

Lambrior<sup>16</sup> found the reaction to be irregular in typhoid fever, as it did not appear in some cases, and in others was alternately negative and positive on different days. He also had positive reactions in many other diseases, but in pleurisies, it was only present in the tuberculous variety. He concluded with Zatzomir<sup>17</sup> that it was of no clinical value.

Seuffert<sup>18</sup> emphasizes the difficulty in discriminating between greens and greenish-blues. Using Russo's method in a large series of cases of tuberculosis, he obtained positive reactions in many cases, but he does not consider it of much absolute value. In another large series of various diseases, not including typhoid fever, a negative reaction was always present.

Rolleston<sup>19</sup> found the methylene-blue reaction positive in forty-four out of fifty-four cases of typhoid fever, using the method of Russo. Of the ten negative cases, eight were convalescent and two were very mild cases. Positive reactions were obtained occasionally in lobar pneumonia, bronchopneumonia and scarlet fever. In a large variety of diseases, the reaction was constantly negative. He regarded it as an excellent indicator of a relapse, and also claimed that its disappearance during the course of an attack was due to a lack of function of the kidney. The filtration of the urine to remove phosphates and urates is advised by him. He regarded the test as of marked diagnostic value due to its simplicity and its early appearance, even before the Widal reaction.

Boggs<sup>20</sup> states that "Russo's methylene-blue test has been shown to be absurd and deserves no further notice."

Rolph and Nelson<sup>21</sup> have recently published a report of their researches as performed at the Toronto General Hospital. For a year they employed it as a routine proceeding in the hospital and vouch as to its efficacy as a diagnostic aid in typhoid fever, if applied early in the disease. Of fifteen patients examined, thirteen gave a positive Russo, eight of these gave a positive diazo, and seven a positive Widal. Two

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16 Lambrior, A. A. Note sur la reaction au bleu de methylene en urologie et sa valeur clinique. Bull. soc. d. med. et nat. de Jassy, 1905, xix, 202 and 263.

17 Zatzomir, V. D. Thesis. La Reaction au bleu de methylene et sa valeur clinique. Jassy, November, 1905.

18 Seuffert, O. Kritische Untersuchungen uber den Ersatz der Ehrlich'schen Diazoreaktion durch die Russo'sche Methylenblaureaktion. Heidelberg, 1906, J. Horning.

19 Rolleston, J. D. The methylene blue reaction of Russo in enteric fever. Med. Press and Circ., London, n. s., 1906, lxxiii, 303, also Transvaal Med. Jour., 1906-7, ii, 268.

20 Boggs, T. R. Laboratory Methods in the Diagnosis of Typhoid Fever. Old Dominion Jour. Med. and Surg., Richmond, 1908-9, viii, 161.

21 Rolph, F. W. and Nelson, W. H. Some Experiences with Russo's Typhoid Fever Test. Med. Sentinel, Portland, Ore., 1910, xxx, 449.

cases reacted negatively to all three tests. One of these, however, gave a positive blood culture and had typical symptoms. The other was an unusual case. The method of Russo was employed, and any urine containing bile was discarded, as it gives a green reaction which cannot be distinguished from the positive reaction. They paid especial attention to diseases simulating typhoid fever in their onset, as influenza, endocarditis and slight septic cases, but the reaction was constantly negative. They regard the cause as a reduction process due to the presence of unknown bodies in the urine. They did not find the gradually returning bluish tinge of much assistance in prognosis, as so many of the dangers of typhoid fever are, as it were, accidental, and not due directly to the severity of the infection.

The following has appeared in the literature since the report of Rolph and Nelson, all observers using the method of Russo.

Lemaire<sup>22</sup> agrees with the conclusions of Cousin and Costa, et al that the test is of no clinical value and that it is simply a physical phenomenon. He also states that it disappears after decolorization with lead acetate and charcoal. Rolph and Nelson's conclusions are not confirmed. Peskova<sup>23</sup> agrees with Lemaire.

Grover<sup>24</sup> does not consider the methylene-blue reaction of value, particularly when compared with the blood-culture. He did not find it positive in all cases of typhoid fever, but found it positive in many non-typhoid cases.

Rankin<sup>25</sup> concludes that the Russo reaction appears positive in typhoid fever, pneumonia, measles and empyema and occasionally in scarlet fever and other diseases, but considers it of some diagnostic value in typhoid fever. He states that it appears more frequently than the diazo reaction, that its intensity indicates the severity of the infection, but disagrees with Rolph and Nelson that it is a good indicator of a relapse or of lysis. It is not pathognomonic of typhoid fever.

Ker<sup>26</sup> (quoting Rankin) thinks unfavorably of the Russo test and considers it inferior to the diazo reaction.

Gambill and Hawley<sup>27</sup> found the Russo reaction positive in eleven cases of typhoid fever and negative in all other cases, except in tuberculosis occasionally. They recommend it because of its early appearance,

22 Lemaire, P. Reaction de Russo et fièvre typhoïde. *Gaz hebdomadaire de médecine et de Bordeaux*, 1912, *xxviii*, 124.

23 Peskova, A. The Russo Reaction. *Med Obozr*, 1911, *lxxvi*, 155.

24 Grover, A. L. The Value of Russo's Typhoid Fever Test. *Boston Medical and Surgical Journal*, 1912, *clxvi*, 706.

25 Rankin, T. T. Russo's Methylene Blue Reaction. *Hospital*, London, 1911-1912, *li*, 87.

26 Ker. *Manual of Infectious Diseases*, 1910.

27 Gambill, W. H., and Hawley, M. C. Russo Reaction in Typhoid Fever. *Illinois Medical Journal*, Springfield, 1912, *xxi*, 592.

before the Widal or diazo reactions, its appearance in some cases in which the Widal and the diazo reactions are never positive, and on account of its simplicity. Drugs had no effect, nor had boiling sufficient to coagulate albumin. Their cases occurred in an epidemic in the Watertown State Hospital, and they were able to eliminate many cases by this simple test, while a blood examination in so many cases would have been no light task.

Hager<sup>28</sup> (quoting Gambill and Hawley) considers the methylene-blue reaction more accurate than the diazo reaction, and states that the color disappears on prolonged boiling.

#### AS A CONFIRMATORY TEST

Williams<sup>29</sup> concludes that the Russo reaction is valuable, especially when used in conjunction with the Widal and diazo reactions. Deductions from the use of all three, he claims, will clear up many misty diagnoses. He advises the use of all three every five days during the course of the disease. His table of conclusions is appended below.

Bouchot, Bovier and Malespine<sup>30</sup> found the reaction positive in fifteen out of seventeen cases of typhoid fever, in two out of three relapses, and consider it to be of good diagnostic value, except that it is occasionally found in other diseases, as measles, erysipelas, salpingitis, pulmonary tuberculosis, acute gastric indigestion, tubercular meningitis and pneumonia. It is not due to albumin nor urates, nor to the fever, as it was negative in many febrile cases. Its appearance in such diseases as pneumonia, erysipelas, measles and small-pox does not materially lessen its clinical value, as the clinical signs of these conditions are sufficient to make a differential diagnosis. Its appearance in tuberculosis and acute gastric indigestion is, however, not favorable. They state that the positive reaction is present in practically every case of typhoid fever, appearing usually as early as the second or third day.

Wallis<sup>31</sup> concludes, after observation in many different diseases, that it is very valuable in the diagnosis of typhoid fever, and is more reliable than the diazo reaction. He advises the use of a control of normal urine and emphasizes the difficulty of detecting the proper color, at first. He agrees with Russo as to its prognostic import. It was found occasionally in measles, small-pox, chronic and suppurative tuberculosis. He never found it positive in acute miliary tuberculosis, and therefore considers it of special value in differentiating that condition from typhoid fever.

28 Hager. *Zentralbl f inn Med*, 1905, p 1100

29 Williams, B G R. *The Widal, Diazo and Russo Reactions in Typhoid Fever—An Interdependence*. *Arch Diag*, 1912, v, 53

30 Bouchot, Bovier and Malespine. *Valeur diagnostique de la reaction de Russo dans la fièvre typhoïde*. *Lyon méd*, 1912, cxix, 103

31 Wallis, R L M. *Methylene Blue Test for Typhoid Fever*. *St Barth Hosp Jour*, 1912, xix, 134

## AUTHOR'S MODIFICATION

It is not the purpose of this paper to discuss the value of the diazo reaction of Ehrlich, nor to compare it with the Russo methylene-blue reaction. However, as most of the foregoing authors have made a com-

TABLE 1—OCCURRENCE OF REACTIONS IN TYPHOID FEVER

	Widal	Diazo	Russo
Appears when?	Appears in typhoid fever usually after first week	Appears early in typhoid fever	Appears early in typhoid fever
Relapse and complications	Relapses and complications appear to have no effect on the reaction	Reappears with relapses, but not with complications	A positive reaction which grows in intensity probably indicates a grave or fatal issue
Is the technic difficult?	Several methods. Some difficult, others fairly simple	Technic simple	Technic exceedingly simple
Reaction time?	Observation of from 2 to 24 hours necessary	Technic rapidly completed	Technic rapidly completed
Acute military tuberculosis?	Never present in this disease	May appear in this disease	Perhaps never present
Always present in typhoid?	No	No	No
In measles?	No	Sometimes	No
In pneumonia?	No	Sometimes	?
In malaria?	No	Sometimes	No
In small pox?	No	No	Yes
Chronic tuberculosis?	No	Yes, often occurs late in fatal cases	Yes
Effect of drugs taken internally?	None	It is probable that no drug taken internally gives the true diazo reaction, although the differentiation of these pseudoreactions may require some skill. Certain of these drugs may interfere with the positive test.	The positive reaction seems to be given by several drugs, notably hexamethylenamine
Reaction late in typhoid?	The rule	The diazo test which makes its first appearance after the second week, points to military tuberculosis. When a positive reaction suddenly appears during convalescence a relapse is expected.	?
Persistent reaction in typhoid?	Gives no prognostic or diagnostic information	May persist throughout infection without any special significance	Persistent reaction probably spells a bad prognosis

parative study of the two, a few facts might be stated in passing. The diagnostic and clinical value of the diazo reaction of Ehrlich is considered superior to the methylene-blue reaction of Russo by all of the authors quoted above except Seuffert, Wallis, Hager, Rankin, Rolleston and Rolph and Nelson, who consider them of equal value. Seuffert points

out particularly the difficulty of properly reading the results of a diazo reaction. He states that it often becomes a matter of personal judgment. Rolph and Nelson, Wallis, Hager and Rankin even place the value of the methylene-blue reaction above that of the diazo reaction. Several of the observers, working with thoroughly decolorized urines, obtained negative diazo reactions in urines which had been positive before decolorization.

The facts published by Rolph and Nelson apparently give a clinical value to this reaction which has been previously overlooked. Stimulated by this very successful report, the reaction was instituted in the Georgetown University Hospital, using the method of Russo. Shortly after this, Dr. Behrend suggested that larger quantities of both the urine and reagent should be used. Acting on this suggestion, a modification and, if possible, simplification of the original technic was attempted, and a satisfactory one was evolved. This modification has been used at the Georgetown University Hospital, the Garfield Memorial Hospital and in many private cases. In all, over twenty-five hundred specimens of urine have been examined, in about one thousand different cases. During the time of these observations, all specimens coming to the laboratories were used, no discrimination being made. Special attention was given to diseases simulating typhoid fever and to all septic cases.

#### TECHNIC

The modified technic, as used in this series, is as follows:

Make an aqueous solution of methylene blue of such concentration that when thoroughly mixed, it will just be translucent. Using the ordinary test-tube, use a sufficient quantity of the methylene-blue solution to fill the test-tube just above the bowl. Then fill the test-tube with urine, and after thoroughly mixing, examine against a good daylight and note the color reaction. Emerald or mint green indicates a positive reaction, while any tinge of blue renders it negative.

The modified technic is advantageous because it simplifies the preparation of the reagent, it obviates the necessity of using exact quantities, and especially it gives a larger quantity of fluid by which the correct color may be judged. It might be added that the solution of methylene-blue keeps indefinitely without apparently undergoing any changes.

It is a fact, not to be disputed, that the correct reading of a color reaction is a very difficult matter in most instances, and in many becomes a matter of personal interpretation. The differentiation of greens from greenish-blues and some light blues very frequently becomes difficult. This difficulty was experienced in making these tests, and although appearing very simple in actually making the reaction, the proper interpretation, nevertheless, becomes a matter of experience. An ability accurately to distinguish colors is, of course, essential. The whole



procedure is facilitated by the use of a larger quantity of fluid, and by the use of a control in the beginning. The latter can readily be made by using a bile-containing urine which produces a clear emerald green. Too much emphasis cannot be laid on this color differentiation, as it is probably in this particular that many of the earlier observers were in error. When only 5 c.c. of the combined fluids are used, it is practically an impossibility properly to divide a series of colors that so closely simulate each other. The color to be obtained is an absolutely clear emerald or mint green, the slightest tinge of blue immediately indicating a negative reaction. It is in this detail of the test that a perfect judgment of colors, gained by experience and the use of a control, is absolutely essential. Closely observing these precautions, a number of dark urines were diluted and light urines were concentrated, and in no instance did a previously positive urine become negative, or *vice versa*.

Certain urines must be eliminated in testing for this reaction, as they produce a green which is of no clinical importance. As stated by Rolph and Nelson, those containing bile must be discarded, and as noted in this series, those containing blood must also be discarded. Urines rendered cloudy by phosphates, urates, etc., should be filtered.

#### RESULTS WITH MODIFIED RUSSO REACTION

In this series of one thousand different cases, the only diseases showing a constant positive reaction were typhoid fever and malaria. A few positive reactions were obtained in other diseases, but these were not very numerous.

There were forty-six cases of typhoid fever examined, in which forty-one gave a positive methylene-blue reaction. Of the five negative cases, the temperature in one had been normal for five days and in another it had been normal for two days. The urine of the third patient was neutral in reaction, and after acidification with acetic acid, a positive reaction appeared. This same case showed a positive reaction later when a relapse occurred. Of the other two negative cases, one was a very mild one. Of the forty-one positive cases, two never showed a positive Widal reaction, twelve did not show a positive Widal until a number of days after the appearance of the methylene-blue reaction, and twenty-nine were positive to both tests. In the last-mentioned twenty-nine cases, one had an intercurrent lobar pneumonia with failure of resolution and another was complicated by bronchopneumonia. Still another was a case of pulmonary tuberculosis with an intercurrent typhoid infection. Russo's observation regarding the gradual return of the bluish tinge during convalescence was confirmed. Its prognostic value is to be doubted, for, as stated by Rolph and Nelson, the dangers of typhoid fever are due in the greater part to accidents. It does, however, emphasize

the necessity of using the test early in the disease, as it usually appears in the first two or three days of the disease. Its constant reappearance in relapses in the above cases, gives it some value in this respect.

Of nine cases of malaria, seven of the tertian and two of the estivo-autumnal types, all gave a positive reaction. However, a negative reaction was quickly obtained on the fall of temperature after treatment with quinin. The fact that a positive reaction is found constantly in typhoid fever and malaria does not seem to lessen its clinical value, as a differentiation is usually easily made by the clinical signs and symptoms, the blood examination and the therapeutic test.

The other diseases examined in this series, and in which a negative reaction was obtained, except in a few cases, are endocarditis, influenza, interstitial and parenchymatous nephritis, localized and diffuse peritonitis, tuberculous peritonitis, acute gonorrheal urethritis, gonorrheal arthritis, post-operative fever, slight and severe septic fevers, septicemia, pulmonary tuberculosis, tuberculous adenitis, tuberculous osteomyelitis, lobar and lobular pneumonia, erysipelas, measles, scarlet fever, chicken-pox, mumps, syphilis, sarcoma, carcinoma, benign tumors, gastric ulcer, gastritis, gastro-enteric intoxication, anemia, acute articular rheumatism, phlebitis, gangrene, exophthalmic goiter, diabetes, cystitis, tonsillitis, bronchitis, abortion, pregnancy, cirrhosis of the liver, appendicitis, and in many healthy individuals, a number of whom had received the course of typhoid prophylactic vaccination.

A few positive results were obtained in the above, namely, one case of acute articular rheumatism, two cases of lobar pneumonia, one case of pregnancy which was afebrile, two cases of abortion which were afebrile, one case of post-operative fever, two cases of acute pneumonic tuberculosis, one case with an irregular fever, in which the Widal was negative, in which no blood-culture was made and in which no definite diagnosis was made, and one case of cirrhosis of the liver. Other cases of these same diseases were carefully examined, but at no time was a positive reaction present, except in the above noted instances.

#### RECAPITULATION

The following facts are stated above, but to recapitulate for a moment. Many observers state that decolorization changes a positive to a negative reaction, and likewise others state that it affects the diazo similarly. Furthermore, surely such strenuous decolorization as with lead acetate and charcoal must cause some chemical changes. The statement that all dark or concentrated urines give positive results is incorrect, as observed in this series, using larger quantities of fluid. The concentration of light urines and the dilution of dark urines did not change the reaction previously obtained.

The opinions of the different observers regarding this test seem to have run almost the complete gamut. On one hand a small minority attach considerable clinical importance to it, while on the other hand, a large majority relegate it to the scrap heap as worthless. Very few have taken the middle ground, as in this paper, regarding this test simply as one link in the chain of evidence, the object of which is to make a correct diagnosis. Very few laboratory tests are absolutely pathognomonic of a specific disease, this one being no exception, and likewise a diagnosis is seldom, if ever, made on a single symptom or test. It is simply by the ability to obtain all the facts bearing on the case that logical conclusions are reached, and a correct diagnosis made. Williams<sup>32</sup> very aptly states that many tests are of no avail because they are not properly interpreted. He points out that in bacteriological work, it is the positive results that are valuable, as finding the tubercle bacillus in the sputum. I quote him below regarding the chemical reactions.

It is the negative chemical reaction which is of the most value. A urine, which on repeated tests, fails to show serum albumin probably is not secreted by an inflamed kidney, and the physician is thus spurred on to search for further cause of the trouble.

With these limitations in mind, we have recourse to a host of valuable short cuts when approaching a case difficult of diagnosis. For example, here is a patient with a fever probably caused by the typhoid bacillus, but the Widal reaction is as yet negative, and a diagnosis cannot be made without further evidence. Holding in mind this patient, let us consider for a moment the chemical urinary test devised by M. Russo. This is a simple little reaction which may be applied by any physician with a test-tube, some methylene blue and two minutes' time, and the technique of which is repeated so frequently in current medical literature that I have not thought best to give it space here. The lazy physician hoped that the positive reaction would enable him to diagnose all his cases without having to study his patients, and as soon as he was disappointed, he condemned the test in no uncertain language. It is not to be denied that the positive reaction is found elsewhere than in enteric fever, but recalling that it is the negative reaction in clinical chemistry which aids us most, suppose we apply it to the patient mentioned above, hoping that it may serve us as a short cut.

The test is negative. What is our conclusion? If this patient has a fever, this is probably not caused by the typhoid bacillus, and we may as well set about searching elsewhere for the cause of the trouble. Of course, such a presumption is not fair unless the test is repeated at frequent intervals. I have seen this test in its negative phase direct the physician to an abscess of the gall bladder and in another case to a pyelitis.

#### SUMMARY

1. The constant positive reaction in typhoid fever and its rare appearance in other conditions, gives this test marked corroborative value. A negative reaction is very good evidence that the condition is not typhoid fever.

<sup>32</sup> Williams, B. G. R. Some Short Cuts to Diagnosis. *Med Times*, December, 1912, p. 361.

2 Its prognostic value is to be doubted, but its continued appearance in severe cases, and reappearance in relapses is important

3 Its simplicity strongly recommends it, with certain limitations, to wit, that a differentiation of the true greens from the bluish-greens is a matter of practice and experience

4 Its very early appearance will aid in isolating a suspected patient at once, and general prophylactic measures will be instituted

5 The success met with in this series with the modified technic should insure a complete investigation for this reaction

## BOOK REVIEW

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AN INTRODUCTION TO THE STUDY OF INFECTION AND IMMUNITY INCLUDING  
SERUM THERAPY, VACCINE THERAPY, CHEMOTHERAPY AND SERUM DIAGNOSIS  
By Charles E. Simon, M.D., Professor of Clinical Pathology and Experimental  
Medicine, College of Physicians and Surgeons, Baltimore Octavo, 301 pages,  
illustrated Cloth, \$3.25, net Lea & Febiger, Philadelphia, 1912

The immense and rapidly increasing literature on the subjects considered in this book, the novelty of many of the discoveries and the complexity of terminology make commendable efforts at a connected account of the present situation. From his own participation in the subject and his success as a bookmaker, the author of this work was justified in undertaking it. On the whole, he may be congratulated on his success. He has given a fairly adequate view of the theory and practice of the subject. It is especially true of the more "practical" chapters, for in the introductory part the author indulges in a fancy for splitting hairs and for *obiter dicta*. Thus, it seems unnecessary to exalt immunity studies by emphasizing the imperfection of previous knowledge. The folly of such a course is well illustrated when, after the trite and overworked emphasis on the imperfections of art, the author grudgingly admits that it is a debatable point whether the means at Nature's commands are, after all, perfect. He might get some suggestions from a recent paper by Maverick (*Med Rec*, Oct 12, 1912). As the latter says, "What does Nature do for the patient in the stupor of typhoid, with renal calculus, ulcer of the pylorus, a torn cervix, high blood-pressure?" We doubt if it is true, and feel sure that the author cannot prove, that "typhoid fever patients always still pursue the same course which was so well described by the physicians of the middle ages." We are not sure where the author finds his references, but believe that while some medieval physicians, like Nathan Smith at a later period, cared well for their patients, those of to-day pursue a much better course than they did fifty or a hundred years ago.

A similar obscurity surrounds the author's discussion of infection, which has no advantages over the current ideas among thoughtful writers. The same tendency is shown in the discussion of virulence, though in this the practical relations of virulence, the effects of passage through animals and capsule formation are admirably described.

The most important discoveries in immunology are well and clearly described so that the various theories, the terminologies and the important phenomena, like anaphylaxis, active and passive immunity and chemotherapy, are adequately presented.

The most useful preventive and therapeutic methods are well described, chemotherapy is sufficiently described in connection with salvarsan, and the work closes with a clear description of diagnostic methods including the Widal, Wassermann, tuberculin and luetin tests. It will prove a useful guide to physicians, and a convenient reference for advanced workers who are not able to obtain first hand information on all the problems discussed.

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## THE RELATION OF GASTRIC AND DUODENAL ULCER TO VASCULAR LESIONS

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The importance of local disturbances in circulation in the etiology of gastric and duodenal ulcer appears to be a well established fact with the majority of those who have made a close anatomical study of this condition. Still this view seems to be far from generally accepted. Only a short time ago a special committee was organized in Germany for the collective investigation of the causation of ulcer of the stomach. In its circular this committee makes the following statement: "The nature of ulcer of the stomach has not yet been explained. Even if we have been successful in producing gastric ulcers experimentally, with all their characteristic signs, yet the etiology of gastric ulcer in man is practically unknown." Schutz<sup>1</sup> says quite recently:

We still have very incomplete and inaccurate ideas as to its etiology and its development and in this regard have to resort to hypotheses. Even the experimental investigations of gastric ulcer, resumed lately, have not advanced us very much. All these investigations labor under the difficulty that the ulcerations which were produced experimentally resemble the ulcers observed in man in their appearance but not in their course. They have confirmed the old experience that local disturbances in circulation play a part in the production of the ulcers, but they have not been able to give an adequate explanation of their peculiar course.

<sup>1</sup> Submitted for publication in THE ARCHIVES, Feb 19, 1913.

<sup>2</sup> From the Pathological Laboratory, Stanford University Medical Department.

1 Schutz: *Ulcus Ventriculi und Ulcus Duodeni*. Wiener Klin. Wchnschr., 1912, LV, 1513. "Wir betreffen ihrer Aetiologie und Genese noch recht unvollkommene und unklare Begriffe haben und in dieser Hinsicht nach wie vor auf Hypothesen angewiesen sind. Auch die in neuerer Zeit wieder aufgenommene experimentelle Erforschung des Magengeschwurs hat uns in dieser Richtung nicht erheblich vorwärts gebracht. Allen diesen Untersuchungen haftet eben der Mangel an, dass die Kunstlich erzeugten Geschwursprozesse wohl in ihrer Form, nicht aber in ihrer Verlaufsweise sich mit den beim Menschen vorkommenden Geschwuren vergleichen lassen. Sie haben nur die alte Erfahrung bestätigt, dass lokale Zirkulationsstörungen bei der Entstehung der Geschwüre eine Rolle spielen, über die Ursache ihres eigentümlichen Verlaufs haben sie uns keine genügende Erklärung zu geben vermocht."

A very similar point of view is shown in a very interesting article by Aschoff<sup>2</sup> dealing with the mechanical conditions which are of importance in the pathogenesis of gastric ulcer and in which he comes to the following conclusion

At any rate the above mentioned investigations permit of the conclusion that although disturbances of circulation of all sorts are of importance in the development of acute ulcers, their chronic character, their location and their shape depend primarily on mechanical conditions, on prolonged contact with gastric juice at physiologic or pathologic points of narrowing on mechanical friction and stress at the lesser curvature along which the ingesta pass to the pylorus, and do not depend on primary disease of the blood-vessels

Very much the same position is taken by Bolton<sup>3</sup> in England. He says

"The main object of the paper has been to show how, by an extension of an acute ulcer and the secondary inflammatory thickening which affects the same and is a necessary consequence of the untreated condition of the ulcer, a chronic ulcer arises. The funnel shape of an ulcer is not due to the fact that it arises as a result of vascular occlusion; it is merely the result of the mode of spread of the ulcer."

It may not be out of place therefore, to re-state the reasons advanced for the belief that gastric and duodenal ulcers arise primarily from vascular lesions and to add a few personal observations which support this idea.

Virchow first pointed out clearly the apparent relation of local vascular disturbances to gastric ulcer. He states<sup>4</sup> that according to his experience the ulceration is preceded by a hemorrhagic necrosis of the mucous membrane and the disturbance in circulation which is its cause he is inclined to attribute to vascular lesions. He mentions in particular disease and obstruction of arteries. He points out that only a local cause will account for such an exquisitely localized lesion<sup>5</sup> and he is said

2 Aschoff Ueber die Mechanischen Momente in der Pathogenese des runden Magengeschwüres und über seine Beziehungen zum Krebs. Deutsch med Wchnschr, 1912, XXXIII, 494. "Jedenfalls lassen die obigen Untersuchungen den Schluss zu, dass zwar für die Entstehung der akuten Geschwüre Zirkulationsstörungen aller Art, für das Chronischwerden, den Sitz und die Form der Geschwüre aber vor allem mechanische Momente, längerer Stillstandskontakt mit dem Magensaft an den physiologischen und pathologischen Engpässen mechanische Reibung und Schiebung an der Glerkturatur, aber keine primären Gefässerkrankungen heranzuziehen sind."

3 Bolton Origin of Chronic Ulcer of Stomach in Acute Variety of Disease. Quart Jour Med, 1912, v, 429.

4 Virchow Historisches, Kritisches und Positives zur Lehre der Unterleibsaffektionen. Virchows Arch f path Anat, 1853, v, 362. "Eine solche Unterbrechung (der Cirkulation) kann gewiss auf mehrfache Weise geschehen allein ich halte es für richtig, nach dem, was ich gesehen habe, dass sie meistens auf Erkrankungen der Magen Gefässe zurückzuführen sei."

5 The local character of the lesion in gastric ulcer had already attracted Cruveilhier's attention. In his original description of gastric ulcer (Cruveilhier Anat pathol du corps Humain, etc, Paris 1829 1835, v) he exclaims "Mais pourquoi un point, un seule point de l'estomac est il profondément affecté?"

to have pointed to the funnel shape of the ulcers as an additional argument of their relation to the vascular system

Merkel<sup>6</sup> seems to have been the first to publish cases of gastric ulcer in which vascular lesions were actually demonstrated. One of them was that of a woman of about 100 years of age with very marked atheroma and general arteriosclerosis, in whom he found at autopsy an acute perforated duodenal ulcer due to a plainly visible thrombosis of the arteria pancreatico-duodenalis.

The most important work, however, was done by Hauser<sup>7</sup> in 1883, and published in his excellent monograph on gastric ulcer and its relation to carcinoma. Hauser refers to Merkel's cases and recounts a case of his own of a recent gastric ulcer in a woman of 54 years of age. In the sections from the ulcer he found an arteriosclerotic artery filled with thrombus. After a careful analysis of the whole problem he comes to the following conclusions:

The hemorrhagic infarct which precedes the formation of the ulcer results always from a permanent interruption of the circulation in the small arteries which ascend from the submucosa into the mucous membrane. The disturbance in circulation may be caused by embolism or by autochthonous thrombosis or tearing of such an artery. The hemorrhagic infarct is followed by a *chronic* ulcer, only when the disturbance in circulation follows local disease of the blood-vessels of the stomach. In case of local disease of the gastric vessels the ulcer assumes a chronic atonic character, because the development of blood-vessels which is necessary to permit healing cannot occur normally from pathologic blood-vessels. The degree of vascular disease, therefore, determines the more or less chronic character of the ulcer.

The last statement in regard to the chronic ulcer of the stomach is of particular importance, because it is offered as an explanation of the failure to produce *chronic* ulcers by experiments which otherwise confirmed

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6 Merkel. Kasuistischer Beitrag zur Entstehung des runden Magengeschwurs, Wien med. Presse, 1866, vii, 754, 770, Zur pathologischen Anatomie des Magengeschwurs, Wien med. Presse, 1869, \, 913.

7 Hauser. Das chronische Magengeschwür. Sein Verlaufsprocess und dessen Beziehungen zur Entwicklung des Magenkarzinoms. Leipzig, F. C. W. Vogel, 1883. "Der zum Geschwür führende hämorrhagische Infarkt der Magenschleimhaut bildet sich stets infolge einer dauernden Unterbrechung des Blutstromes in den kleinen von der Submucosa zur Schleimhaut aufsteigenden Arterienstämmchen. Diese Cirkulationsstörung kann bedingt sein entweder durch Embolie oder durch autochthone Thrombose oder Zerreissung eines solchen Arterienstämmchens. Zum chronischen Magengeschwür führt der hämorrhagische Infarkt der Magenschleimhaut nur dann, wenn die Cirkulationsstörung aus einer localen Erkrankung der Magen Gefässe selbst hervorgegangen ist. Bei einer localen Erkrankung der Magen Gefässe nimmt das Geschwür deshalb einen chronischen atonischen Charakter an, weil die zur Heilung erforderliche Gefässneubildung von pathologisch veränderten Gefässen nicht in normaler Weise vor sich gehen kann, der mehr oder minder chronische Charakter des Geschwurs ist daher durch den Grad der Gefäßerkrankung bedingt."



Virchow's theory Panum,<sup>8</sup> in 1862, produced an acute gastric ulcer with all its anatomical characteristics by embolic obstruction of one of the arteries of the stomach. Cohnheim<sup>9</sup> perfected the technic by injecting chromate of lead directly into one of the arteriae gastricae which arise from the splenic artery. Animals killed within a few days of the experiment showed typical acute gastric ulcers but all animals killed after the second week showed a normal mucous membrane as an evidence of the remarkable regenerative power of this structure which has been brought out more and more clearly by later experimentation. It is impossible here to enter into the numerous attempts which have been made since to produce gastric ulcers experimentally. Suffice it to say that the latest endeavors in this direction by Payr<sup>10</sup> and by Suzuki<sup>11</sup> are based on Cohnheim's idea. They have been somewhat more successful because in their experiments through the use of injections of hot salt solution, dilute formaldehyd and dilute alcohol (Payr) or of silver nitrate, epinephrin or dilute solution of nicotine (Suzuki), more extensive local vascular lesions have been produced. This practically confirms Hauser's statement in regard to the interdependence of the degree of vascular disturbance and the chronicity of the ulcer. But in these experiments even, the chronic ulcers so produced which may perforate and which may show extensive cicatrization with contraction in their surroundings, heal eventually. It is evidently impossible experimentally to reproduce exactly the conditions as they exist in man, but the resemblance of these experimental ulcers to those in man is very striking.<sup>12</sup>

Hauser made another very important observation. It had been asserted then, and is still frequently asserted now that ulcer of the stomach is most frequently found in young individuals, more especially in young women suffering from chlorosis. This view is based on the clinical experience that such individuals often suffer from symptoms like hematemesis, which are commonly attributed to ulcer. Frequently however, this clinical assumption lacks sufficient justification in fact as is shown by the experience of surgeons who have operated on such

8 Panum. Beiträge zur Lehre von der Embolie. Virchows Arch, 1862, xxi, 490. In a dog he injected globules of black wax through a catheter introduced into the cranial artery and pushed to the lower border of the ribs. The animal died nine and one half hours after the experiment. In the fundus of the stomach he found an ulcer of the size of a hazelnut with black wall and bottom. Wax was found in arteries in the muscle and some in the black margins of the ulcer.

9 Cohnheim. Vorlesungen über allgemeine Pathologie, Berlin, 1880, ii, 53.

10 Payr. Ueber Pathogenese, Indikationstellung und Therapie des runden Magengeschwurs. Deutsch. med. Wchnschr., 1909, xxxv, 1556. Beiträge zur Pathogenese, pathologischen Anatomie und radikalen operativen Therapie des runden Magengeschwurs. Arch. f. klin. Chir., 1910, xciii, 436.

11 Suzuki. Experimentelle Erzeugung des Magengeschwurs, Arch. f. klin. Chir., 1912, xcvi, 632.

12 See photographs in Payr's and Suzuki's papers (l. c., notes 10 and 11).

patients Hauser, looking over the material of the pathological institute at Erlangen, discovered that so far as necropsies show, ulcer of the stomach is not so exclusively or even frequently a disease of the young as had been supposed. In his series the majority of cases occurred after 30. This observation of Hauser's has been later confirmed by much larger statistical material. Oberndorfer,<sup>13</sup> who bases his statistics on 3,412 necropsies, among which there were 239 cases of gastric ulcer or of scars remaining from the same, gives the following table in regard to ages

Age, years	Cases	Age, years	Cases
10-19	5	50-59	49
20-29	21	60-69	55
	—	70-79	33
	26	Over 80	11
30-39	24		<hr/>
40-49	41		213

The preponderance of individuals over 30 is evident. He also makes the significant statement, that in old age one finds not only old ulcers, but frequently fairly recent ones. Oberndorfer's statistics also correct the impression that gastric ulcer is more commonly found in women than in men. He finds exactly the same proportion in both sexes. He also shows that ulcer of the stomach is just as common in Munich as elsewhere, whereas Munich was supposed to enjoy a peculiar relative immunity from this disease. There is perhaps no other disease in which we have been indulging in so many preconceived notions which it is so difficult to eradicate when they are once fairly established. Paus,<sup>14</sup> in Christiania, Norway, on the basis of 100 cases of gastric and duodenal ulcer, estimates the average age in man at 50 $\frac{1}{4}$  years and in women at 48 $\frac{3}{4}$  years.

Hauser was also the first to call attention to the fact that gastric ulcer is frequently associated with general arteriosclerosis, which, of course, supports the vascular theory. This remarkably close association was what called my attention to the matter. In studying arteriosclerosis the rather common occurrence of gastric or duodenal ulcer in arteriosclerotics became so evident that almost unconsciously I began to look on it as a lesion comparable to arteriosclerotic scars in heart and kidneys, and I have so treated it in my paper on subacute and chronic nephritis.<sup>15</sup>

Apart from the peculiar funnel shape of many of the deep ulcers, there is one feature which to my mind points very strongly to a relation of the ulceration to local disease of the arteries. This is the frequent

13 Oberndorfer. Ueber die Häufigkeit des Ulcus rotundum ventriculi in München. München med. Wehnsch., 1909, lvi, 1640.

14 Paus. Statistische Bemerkungen über peptische Ulcerationen. Beil. klin. Wehnsch., 1912, xlv, 397.

15 Ophuls, W. Subacute and Chronic Nephritis as found in one thousand unselected necropsies. THE ARCHIVES INT. MED., 1912, x, 156.

erosion of arteries at the base of the ulcer, followed by severe arterial hemorrhage. If the blood-vessels were merely accidentally opened by a gradual extension of the ulceration into the tissues there is every reason to believe that veins would be more likely to be opened than arteries. This point has really not received the attention which it deserves. One has taken this fact of the frequent erosion of arteries as a matter of course, which it is not at all, and it is astonishing how indefinite the statements in literature are in regard to this phase of the subject. The majority of authors are quite content to repeat Cruveilhier's haphazard statement that severe hemorrhages are apt to come from the splenic artery, which, so far as my experience goes, is very exceptional to say the least. The hemorrhages come from those arteries which supply that part of the gastric or duodenal wall in which the ulcers are situated, that is in the usual position of these ulcers the hemorrhage arises from branches of the *arteria gastrica* or *gastro-epiploica dextra* or of the *arteria pancreatico-duodenalis*. If the ulcer is the result of obstruction of such an artery either by disease or embolism, one understands at once why the necrosis should involve these arteries, and an opening result when the necrotic material is removed by digestion. The wonder is then, not that we have so many severe hemorrhages but that we do not have them even more frequently.

Much has also been said about the abundant blood-supply of the walls of the stomach and duodenum and about the numerous anastomoses between the arteries. As a matter of fact anyone who takes the trouble to dissect the arteries of the stomach will be astonished how poorly supplied with arteries are those parts of the wall of the stomach and duodenum where we usually find ulcers. This is particularly true of the extreme pyloric end of the stomach at the lesser curvature and on the posterior wall, and of the beginning of the duodenum at its convexity. In the living, W. J. Mayo<sup>16</sup> noticed the appearance of an anemic spot on the duodenum on the slightest traction. He says

The arrangement of the blood vessels immediately distal to the pylorus is such that this traction may interfere with the vascularization and the local anemias thus produced causes a white spot to appear on the duodenum just below the pylorus.

Wilkie<sup>17</sup> made a very careful study of the blood-supply to the first part of the duodenum. He finds that the spot described by Mayo is supplied by a small artery of varying origin (the "supraduodenal" artery) which is practically an end-artery. He also states that anastomoses between some other arterial branches which supply the first part of the

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<sup>16</sup> Mayo, W. J. Anemic Spot on the Duodenum which may be Mistaken for Ulcer. *Surg. Gyn. and Obst.*, 1908, vi, 600.

<sup>17</sup> Wilkie. The Blood-Supply of the Duodenum. *Surg., Gyn. and Obst.*, 1911, xiii, 399.

duodenum are by no means free. He mentions in cases of duodenal ulcer the frequency of arteriosclerosis in the arteries which supply the site of duodenal ulcers, and for all these reasons he believes that lack of blood-supply is an important factor in the production of duodenal ulcer.

Payr<sup>18</sup> also calls attention to the frequency of thrombotic or arteriosclerotic obstruction in arteries in resected specimens of human ulcers.

The accompanying tables give the results of my own observations. The cases are unselected ones, found among about 1,500 necropsies.



Fig. 1—Photograph of ulcers in Case I, 18 (XVI-58)

I believe that Table 1 brings out strikingly the frequent coincidence of well-marked general arteriosclerosis with what for want of a better name we may call "chronic gastric or duodenal ulcer in individuals over 30." In all cases in which such an examination was possible a microscopic examination of the arteries at the base of the ulcer showed very marked thickening of the intima, and frequently in addition complete closure

18 Payr. *Deutsch med Wchnschr*, 1909, XLV, 1556. "Die Gefasse finden wir nicht selten in Bereich dieser Starre verandert, sie zeigen Wandverdickungen, Endarteritis, Endophlebitis. Organisation nach thrombotischen Verschlusse."

TABLE 1—CASES OF CHRONIC ULCER OF STOMACH

No	Sex	Age Years	Location and Appearance of Ulcer	Condition of Arteries, Local
1 I 75	Male	Over 60	Shallow chronic ulcer at lesser curvature	Not examined
2 I 77	Male	Over 70	Deep chronic ulcer 1.5 x 1 cm in pyloric region, head of pancreas involved	Not examined
3 I 109	Male	About 40	Deep chronic ulcer 1 x 2 cm in posterior wall of pylorus	Not examined
4 IV 58	Female	Over 60	Deep chronic ulcer size of quarter in posterior wall of pylorus	Not examined
5 IV 71	Male	51	Rather shallow chronic ulcer 6 x 2 cm on lesser curvature and anterior wall at pylorus	Marked arteriosclerosis of small artery at base
6 IV 82	Male	45	Deep chronic ulcer 4 x 2.5 cm on lesser curvature near pylorus	Not examined
7 V 126	Male	55	Deep chronic ulcer 2 cm in diameter on lesser curvature and anterior wall near pylorus	Marked arteriosclerosis of all arteries near ulcer one entirely closed
8 IX 50	Male	61	Deep chronic ulcer 1.5 cm in diameter at pylorus	Not examined
9 IX 58	Male	61	Deep chronic ulcer about 1.5 cm in diameter at pylorus	Not examined
10 IX 67	Male	Over 60	Deep chronic ulcer 3 cm in diameter in posterior wall at pylorus	Marked arteriosclerosis in arteries at base of ulcer
11 XI 28	Male	72	Deep chronic ulcer 1.5 cm in diameter in duodenum 2 mm from pylorus	Not examined
12 XI 41	Female	39	Small chronic ulcer in anterior wall near lesser curvature chronic perforating ulcer in posterior wall of duodenum near pylorus	Not examined
13 XII 38	Female	40	Chronic ulcer 2 x 1 cm in anterior wall about 1 cm from lesser curvature about 10 cm from pylorus	Not examined
14 XIII 14	Male	About 55	Chronic ulcer about 1 x 1.5 cm at lesser curvature half way between cardia and pylorus	Very marked arteriosclerosis in all arterial branches at base of ulcer extending beyond cicatrix
15 XIII 112	Male	45	Chronic ulcer about 1.5 cm in diameter on lesser curvature 5 cm from pylorus	Not examined
16 XIV 16	Male	45	Chronic ulcer on lesser curvature half way between pylorus and cardia	Not examined
17 XV 66	Male	67	Chronic ulcer about 1.5 x 0.75 cm in duodenum about 1 cm from pylorus	Not examined
18 XVI 58	Male	About 50	Two small chronic ulcers about 6 mm in diameter about 6.5 cm from pylorus one on lesser curvature, the other about 2 cm from it on posterior wall	Very marked arteriosclerosis of arterial branches running to ulcer and of arterioles in base of ulcer

Condition of Arteries General	Condition of Aorta and of Heart	Remarks
Marked peripheral arteriosclerosis, large arteriosclerotic scars in heart and kidneys	Marked atheroma of aorta, heart twice normal size	Death from suppurative cholecystitis
Marked peripheral arteriosclerosis, large arteriosclerotic scars in kidneys	Marked atheroma of aorta, atrophy of heart	Death from broncho- pneumonia
Extreme arteriosclerosis of small arter- ies, arteriosclerotic nephritis	Slight atheroma of aorta, concentric hypertrophy of left ventricle	Death from strepto- coccus tonsillitis
Arteriosclerosis of coronaries and arte- riosclerotic scars in kidneys	Marked atheroma of aorta, atrophy of heart	Death from carcinoma of cecum
Slight arteriosclerosis of larger arter- ies, arteriosclerotic scars in kidneys	Slight atheroma of aorta, <i>marked hypertrophy of left ventricle</i> , heart twice nor- mal size	Erosion of artery
Moderate arteriosclerosis of peripheral arteries, arteriosclerotic scars in kid- neys	Slight atheroma of aorta, heart normal	Perforation, local ab- scess, <i>erosion of</i> artery, large hemor- rhage
Arteriosclerosis of splenic and renal arteries	Atrophy of heart	Erosion of artery, large hemorrhage
Marked peripheral arteriosclerosis, necrosis and arteriosclerotic scars in heart, arteriosclerotic softening of brain, arteriosclerotic scars in kidneys	Moderate atheroma of aorta, Heart $\frac{3}{4}$ normal size	Erosion of artery, fatal hemorrhage
Marked peripheral arteriosclerosis with cerebral softening, arterioscle- rotic scars in heart and kidneys	Moderate atheroma of aorta, Heart $\frac{3}{4}$ normal size	Erosion of artery, fatal hemorrhage
Moderate peripheral arteriosclerosis	Normal aorta, normal heart	Erosion of artery, fatal hemorrhage
Marked peripheral arteriosclerosis, arteriosclerotic scars in kidneys	Very marked atheroma of aorta, heart $\frac{1}{2}$ normal size	Death from broncho- pneumonia
Peripheral arteriosclerosis, arterio- sclerotic scars in kidneys	Atheroma of aorta, heart $1\frac{1}{2}$ times normal size	Perforation, acute peritonitis
Moderate peripheral arteriosclerosis, arteriosclerotic scars in kidneys	Moderate atheroma of aorta, heart normal	Perforation, subdia- phragmatic abscess
Moderate peripheral arteriosclerosis, arteriosclerotic scars in kidneys	Aorta and heart normal	Severe local arterio- sclerosis, death in epileptic coma
Marked peripheral arteriosclerosis with multiple thrombosis	Slight atheroma of aorta, marked concentric hyper- trophy of left ventricle	Stenosis of pylorus, dilatation of stom- ach
Marked arteriosclerosis of some per- ipheral arteries, arteriosclerotic scars in kidneys	Slight atheroma of aorta, normal heart	Perforation, local abscess formation
Marked peripheral arteriosclerosis in- cluding large abdominal arteries and branches, arteriosclerotic scars in heart and kidneys	Slight atheroma of abdom- inal aorta, heart $1\frac{1}{2}$ to 2 times normal size	Death from unresolved pneumonia
Marked peripheral arteriosclerosis, small areas of softening in brain, small arteriosclerotic scars in kidneys	Moderate atheroma of aorta, heart $\frac{1}{2}$ normal size	Case of transverse myelitis and chronic pulmonary tubercu- losis

by subsequent thrombosis. These were by far the most numerous cases of gastric or duodenal ulcer (18 out of 23).

One should not, however, imagine that it is always an easy matter to find the diseased artery. Frequently numerous sections must be cut from different places, in other words the whole floor of the ulcer must be studied microscopically, before the diseased artery or arteries are found. It is astonishing how often directly adjoining an almost normal artery one finds another branch which is badly diseased (Fig. 5).



Fig. 2—Photograph of outer surface of stomach in Case I, 18 (XVI 58), showing arteriosclerotic arteries leading to ulcer.

The most interesting case of this series is the last one (No. 18, XVI, 58). Figure 1 gives a picture of the gross lesions. There were in a case of severe general arteriosclerosis, two small almost symmetrical chronic ulcers on either side of the lesser curvature, somewhat nearer the cardia. Figure 2 shows the arteriosclerotic branches of the arteria gastrica which can be traced to the base of both ulcers which are situated at X X. Figures 3 and 4 show sections of these arteries. Figure 3 some distance from the ulcer and Figure 4 the same artery in the cicatricial tissue at the

base of one of the ulcers (I may say that conditions in the other ulcers were very similar) In Figure 4 the arteriosclerotic narrowing is apparently intensified by an additional obstruction with organized thrombus

One question remains to be answered How do we know that the obstruction of the arteries in these cases is primary and not secondary to the chronic inflammatory changes at the base of the ulcers, as has been claimed so frequently? In the first place we can point to a well-marked general arteriosclerosis in all cases which, although frequent at this age, is not so constant that we should expect to find it so regularly and so well

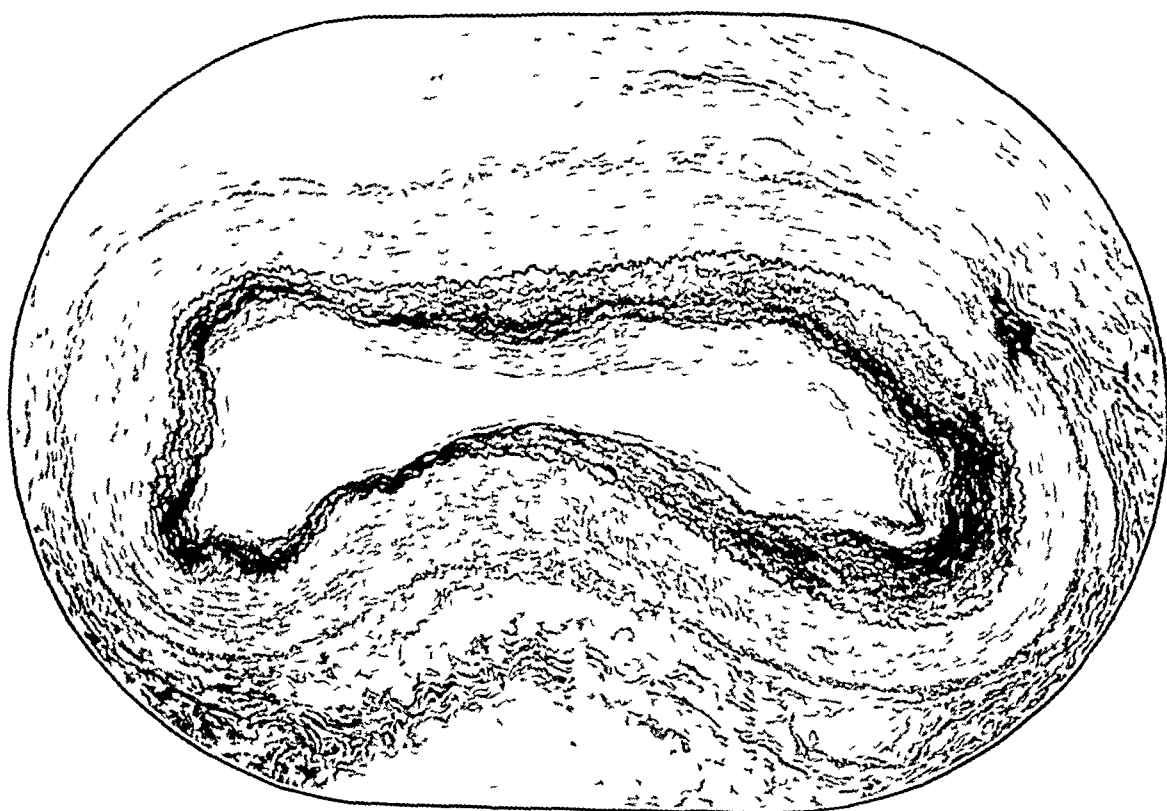


Fig 3—Microphotograph of arteriosclerotic artery in Case I, 18 (XVI-58) near ulcer

developed In the second place, the lesion of the arteries can always be followed up to points well beyond the cicatricial base of the ulcer Thirdly, in a number of cases at least, the lesion is histologically evidently arteriosclerosis as defined by Jones; that is, there is an abundant splitting up of the elastic membrane between intima and muscle and much new-formation of elastic tissue (Figures 3 and 4) But even in those cases in which this is not so evident, I still believe that we have to deal with arteriosclerotic lesions as distinct from local endarteritis The condition represented in Figure 5 is almost conclusive on this point This photograph shows a rather cellular intimal thickening in a branch of one of the gastric arteries without any new formation of elastic tissue





Fig 4—Microphotograph of arteriosclerotic artery in Case I 18 (XVI-58)  
Note cicatricial tissue at base of ulcer

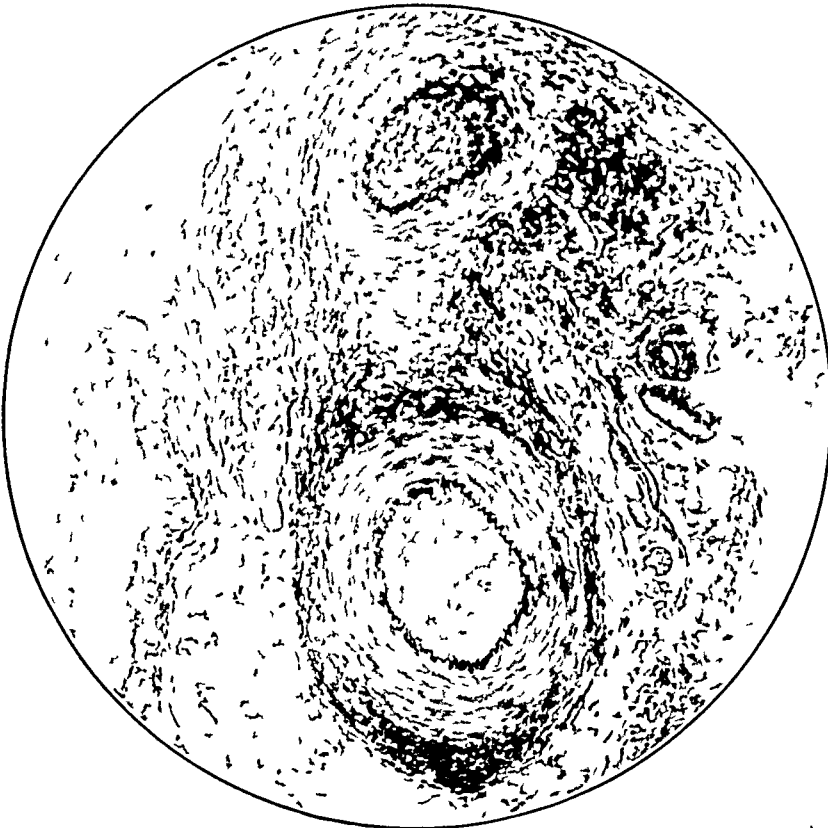


Fig 5—Microphotograph of arteriosclerosis of branch of gastric artery without hyperplasia of elastic tissue in case of general arteriosclerosis without gastric ulcer (Case P, 371)



Fig 6—Microphotograph of diseased artery ending abruptly on floor of ulcer in Case I, 10 (IX 67)

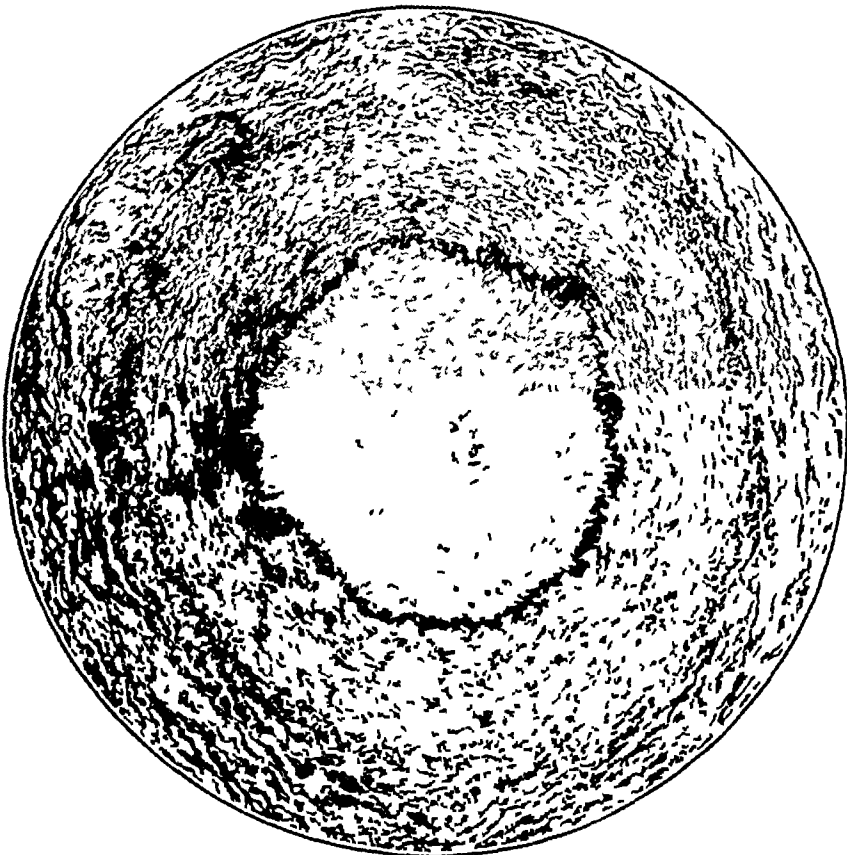


Fig 7—Microphotograph of cellular intimal thickening in artery some distance away from ulcer in case of gastric ulcer in a young man (Case II, 3, VII-93 )

in a case of general arteriosclerosis. There was no gastric ulcer present in this case, therefore no local inflammation which could produce endarteritis. This case is also particularly interesting because there was a small scar in the outer layer of the muscular wall of the stomach at the point supplied by the obstructed artery. In other words, a lesion absolutely identical in origin with an arteriosclerotic scar of the heart muscle.

TABLE 2—CASES OF CHRONIC ULCER OF STOMACH

No	Sex	Age Years	Location and Appearance of Ulcer	Condition of Arteries, Local
1 III 91	Male	33	Deep chronic ulcer 1 cm in diameter at pylorus over head of pancreas	Marked arteriosclerosis
2 V 88	Male	24	Old scar and perforating ulcer 1 cm in diameter in duodenum near pylorus	Marked "acute" arteriosclerosis of all arteries near ulcer and scar
3 VII 93	Male	39	Shallow chronic ulcer 3.5 cm in diameter on lesser curvature 5 cm from pylorus	At base large artery almost obliterated by "acute" endarteritis
4 XV-131	Male	30	Chronic perforating ulcer about 1.5 cm in diameter in wall of duodenum 2 mm from pylorus	*

\* No arteriosclerosis in some of the arteries in scar but at base of ulcer one artery and

TABLE 3—ACUTE EMPHATIC

No	Sex	Age Years	Location and Appearance of Ulcer	Condition of Arteries Local
1 XIV-30	Male	65	Acute deep ulcer about 6 x 1.5 cm in posterior wall of duodenum directly adjoining pylorus, pin areas exposed	7

7 At base of ulcer small perforated artery which is blocked by easily detached piece of

Figure 6 taken from another case, is of some interest on account of the suggestive way in which the obstructed artery opens up on the surface of the ulceration. The artery is eroded from in front and not from the side. I have found many such places in my specimen sometimes several in one ulcer.

In regard to the reasons why such ulcers should become chronic I have very little to add to Hauser's arguments. It is merely a matter of malnutrition of the adjoining tissues which prevents regeneration and which we cannot imitate in our experiments on animals.

My impression is that such arteriosclerotic ulcers in persons over 30 heal very rarely, and, from what I can gather from literature, they are extremely refractory to treatment

The second group of ulcers (11, 1-4) in young individuals is quite different. There is no, or very little, general arteriosclerosis. The arteries show a local, usually quite cellular, endarteritis as shown in Figure 7. In

#### IN THE YOUNG WITH LOCAL ARTERIOSCLEROSIS

Condition of Arteries General	Condition of Aorta and of Heart	Remarks
Small arteriosclerotic scars in kidneys	Atrophy of aorta and of heart	Stenosis of pylorus, dilatation and hypertrophy of stomach
Apparently normal	Apparently normal	Severe local arteriosclerosis, perforation, acute peritonitis
Slight peripheral arteriosclerosis	Slight atheroma of thoracic more marked of abdominal aorta, normal heart	Severe local arteriosclerosis, fatal hemorrhage
Slight peripheral arteriosclerosis	Heart and aorta small	Severe local arteriosclerosis, perforation, fatal peritonitis

its branches practically occluded by arteriosclerosis

#### ULCER OF STOMACH

Condition of Arteries General	Condition of Aorta and of Heart	Remarks
Slight peripheral arteriosclerosis	Slight atheroma of aorta, heart $\frac{3}{4}$ normal size	Acute embolic ulcer, fatal hemorrhage

thrombus (embolus-thrombi in left heart and in aorta)

these cases the question whether the arterial disease is primary or secondary is much more open to discussion, although I am inclined to believe, that in such instances also one is dealing with a local primary disease of the arteries like that which nobody denies to exist in cases of spontaneous gangrene of the leg in young individuals. The one strong reason in favor of this view is that the disease in the arteries in these cases also usually extends a good distance beyond the base of the ulcer as shown in Figure 7.

Here also, as in the case of early gangrene, the question arises whether the intimal thickening is primary or secondary to thrombosis. The few cases at my disposal hardly justify any final conclusions in this regard.

It is quite likely that ulcers of this second group have a more marked tendency to heal, unless the individuals die from perforation or from hemorrhage although in Case 11, Table 1 a definite stenosis of the pylorus was produced by one of them. It may be that "Tyson" has such cases in mind when he says:

I consider the division between acute and chronic ulcer much more marked than Sir Bertrand Dawson has admitted. I have seen some 300 cases of gastric ulcer during the last thirty years and have watched their progress. With regard to cases of gastric ulcer under 25 if they do not die suddenly from hemorrhage and perforation they invariably get well whereas the chronic cases after 30 form another class consisting as often if not more often of men as of women.

I do not think it is well to distinguish these two groups as acute and chronic ulcer although there is some truth in this distinction. I should prefer to speak of them as the gastric (or duodenal) ulcer of the young and as the arteriosclerotic ulcer of later life.

Case 31 is a typical case of acute embolic ulcer of the duodenum with fatal hemorrhage. Such ulcers have been frequently described in literature especially after burns and after operations (I myself observed another case after hysterectomy) and are generally conceded to be due either to embolism or thrombosis as the case may be.

#### CONCLUSIONS

From the above I believe we are justified in drawing the following conclusions:

- 1 The most common type of gastric (or duodenal) ulcer, at least in material obtained by necropsy, is the arteriosclerotic ulcer in persons over 30 years of age.

- 2 There is a second class of gastric (or duodenal) ulcer in the young, which is probably due to local endarteritis (thrombo-arteritis<sup>2</sup>).

- 3 In addition to these, one occasionally observes acute embolic (or thrombotic) ulcers.

Sacramento and Webster Streets

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19 Tyson. Discussion on Gastric Ulcer. Brit Med Jour. 1912, ii 950

# EFFECT OF CHANGE OF POSTURE—WITHOUT ACTIVE MUSCULAR EXERTION—ON THE ARTERIAL AND VENOUS PRESSURES

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In this consideration we present the results of our investigations on the effects produced by change of posture, when this change is brought about without effort on the part of the subject. It is, of course, understood that in the standing posture there is exerted a constant muscular effort, while in the horizontal posture this element is eliminated.

## METHODS

Our subjects were placed on a table with a movable top. This top was set and balanced so that when the subject was once placed in position, he had no further occasion for voluntary muscular effort. After stepping onto the foot-board of the table, which was about 6 inches above the floor, the arm-pieces of the blood-pressure instruments were attached. The instrument for arterial pressure was of the usual type, mercury column, cuff 10 cm wide. The apparatus for measuring the venous pressure was that of the type constructed by Hooker and Eyster, which is a modification of the one by Von Recklinghausen. The cuff of the arterial pressure apparatus was applied to the right arm at the heart level, the venous measuring attachment, to the left arm whenever possible, at the level of the axilla. The arterial pressure readings, maximum and minimum by the auscultatory method, were made one every minute, beginning on the minute, for five consecutive minutes. After the fifth reading, the venous pressure was estimated. The venous pressure reading finished, the subject was instructed to lean back in a completely passive way, on the table board. He was then tilted to the horizontal posture, and the table top was fastened down with a chain. In most instances it would not have been necessary to fasten the board on account of the balancing toward the upper half of the table. Five consecutive readings of the maximum and minimum pressures were made in this posture, and about half a minute after the last arterial reading the venous pressure was estimated. The table was gradually retitled to the erect posture when five arterial readings and one venous estimation were again made.

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\* From the Department of Student Health, Carnegie Institute of Technology

We presumed that five minutes was a sufficient length of time for the circulation to orient itself in response to the effects of this change of posture, and by eliminating as much as possible, the active muscular effort, we expected results that would be of easier interpretation than when the subject exerts himself in changing his postures.

*Material* — The forty-eight subjects of these experiments were students at the Carnegie Institute of Technology, their ages varied between 15 and 30 years. About one-third of these were members of the various athletic teams. Their state of health, their muscular development, the condition of their hearts and their strength tests all enter into this consideration and will be, respectively, considered as influential factors in the behavior of the circulation as it responds to changes in posture.

*Arterial Pressures* — The height of the maximum arterial pressures in this series was at the usual level. A curve based on the ages of the subjects would show a gradual increase with the advance of years.

In comparing the regularity of the maximum and minimum pressures we find that the minimum pressure level is more constant—is subject to less variation than the maximum.

It is interesting to note in the individual cases how much fluctuation in the blood-pressure actually takes place each minute under psychic influences. We have eliminated almost every other element in these experiments except this one, which is largely a matter of personal equation. The error due to this is inherent in all work, on the healthy and diseased, on the strong and the weak. So far as the reliability of the total results is concerned, we believe this to be a negligible factor, particularly since we carried the experiments over a five-minute period. The illustrations show this constant oscillation of the arterial pressures.

*Venous Pressure* — The venous pressure readings were taken whenever possible on the arm at the level of the subcostal angle, i. e., at the level of the right auricle. Such were the only cases included in our series on which we base our figures of what constitutes an average normal venous pressure.

Our findings in those cases in which we had to make our readings below or above the level of the auricle did not always show a constant relative difference comparable to the distance above or below the mark. In that respect our observations do not bear out those of other investigators.

In our observations on the effect of change of posture on the venous pressure, all our readings are included, since the absolute height of the venous pressure did not enter into the consideration.

*Pulse Pressure* — With the advent of the auscultatory method for estimating the maximum and minimum arterial pressures, we were more

certain of our readings in this work than with the graphic method as interpreted by the Erlanger instrument in our former work. The auscultatory method has made the investigation of the pulse pressure accessible for clinical study as well as physiological research and we may hope for valuable information as the evidences accumulate.

#### ARTERIAL PRESSURES OF THIS SERIES

The height of the maximum pressures ranged between 95 and 140. The minimum pressures between 65 and 92 mm. As previously noted, the greater variation occurs in the maximum pressure, and both maximum and minimum blood-pressure rise with the advance of years (Fig 1).

In twenty-two of these cases we have the strength test for comparison and study. The test consists of measuring according to the inter-collegiate standard.

In those whose strength total ranged between 704 and 541 kilo, the average maximum pressure in the erect posture was 124.26, the average minimum pressure was 79.35, the pulse pressure 44.91, while in those

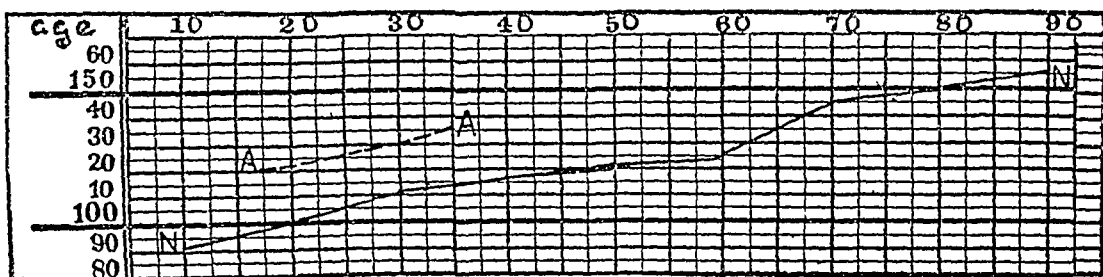


Fig 1—Chart showing averages of blood-pressure at different age periods. The line A-A indicates a higher than average blood-pressure in trained athletes.

whose strength tests varied between 505.4 and 355.9 kilo, the average maximum pressure was 120.57, average minimum pressure 74.61 and average pulse pressure was 45.96.

These figures will tend to show that the stronger individuals have higher blood-pressures. This is not entirely true, for the circulation of some of our very best athletes, who are actually human towers of strength and endurance, goes along easily and quietly with a low blood-pressure. Such a one is in fact the best type of athlete. But in a series of athletes we meet with many who have trained up to a point of efficiency, and in that training have developed a compensatory hypertrophy. It is these who have higher than average blood-pressures, and these occur frequently enough to bring up the average. (See Line A—A, Fig 1.)

*Effect of Change of Postures on Arterial Pressures*—The blood-pressure readings, as previously stated, were taken on the minute for five consecutive minutes, first in the erect, then in the horizontal, then again in the erect postures. In studying the effect of change of posture on the



behavior of the arterial pressures, we thought it advisable to extend the readings over a period of five minutes. The pressure readings over these five minutes were averaged and Table 1 shows the results of the change of posture.

The conclusions to be drawn from these observations are: When the element of active muscular exertion has been eliminated, the manner in which the circulatory system responds to the effect of bodily posture, under the stated conditions, is as follows: In changing from the erect to horizontal the maximum pressure will usually be increased, the minimum pressure will almost always be diminished. When the erect posture is resumed, the maximum pressure will almost invariably fall and the minimum almost invariably rise. In the falling of the maximum pressure, when the erect posture is resumed, it will nearly always fall considerably below the previous height of the first reading while the minimum pressure may be higher or lower than the first reading with almost equal frequency (Table 1).

TABLE 1—EFFECT OF CHANGE OF POSTURE ON MAXIMUM AND MINIMUM PRESSURE

Maximum Pressure			than	Minimum Pressure			than
Erect	Horizontal	Erect	First	Erect	Horizontal	Erect	First
×	28+	7+	8+	×	1+	13+	25+
	20—	40—	38—		41—	1—	21—

First column × = height of maximum pressure in erect

Second column + = increase of maximum pressure when changed to horizontal

Second column — = fall of maximum pressure when changed to horizontal

Third column — = fall of maximum pressure when changed to erect

Third column + = rise of maximum pressure when changed to erect

Fourth column — = the height of maximum pressure was lower when the erect posture was resumed, than the first readings in the erect

Fourth column + = height of maximum pressure greater than first

Columns 5, 6, 7, 8 read in same way as 1, 2, 3, 4

#### PULSE PRESSURES

The pulse pressures in this series, in the erect posture ranged between 15 and 72 mm Hg, the average for the series being 36.46. It was greater in the cases in which the maximum pressure was higher.

Arranged according to age of the subjects, the pulse pressure in the erect posture in those between 16 and 21 years was 37.1 mm, while those between 21 and 30 years was 40.61 mm.

*Effect of Change of Posture on Pulse Pressure*—Change of posture from the erect to horizontal caused an increase in forty and a fall in seven. From the horizontal to erect caused a decrease in forty-one and an increase in four. In the fall from the horizontal to erect, the pulse pressure fell lower than it was at the first reading in the erect, in thirty-four cases. It remained higher than the first reading in eleven cases. The pulse pressure seems to vary in the same direction as the maximum pressure.

*In the Strongest Half of the Series*—On change from the erect to the horizontal, the maximum pressure was increased in seven and diminished in four. From the horizontal back to the erect, it was diminished in nine and increased in two.

In this fall the maximum pressure reaches a lower level than it was at the first reading in the erect in ten cases out of eleven.

The minimum pressure, in this series, from the erect to horizontal, fell in nine and rose in two. From horizontal to erect, it rose in ten and fell in one. This rise was to a higher level than the first reading in six

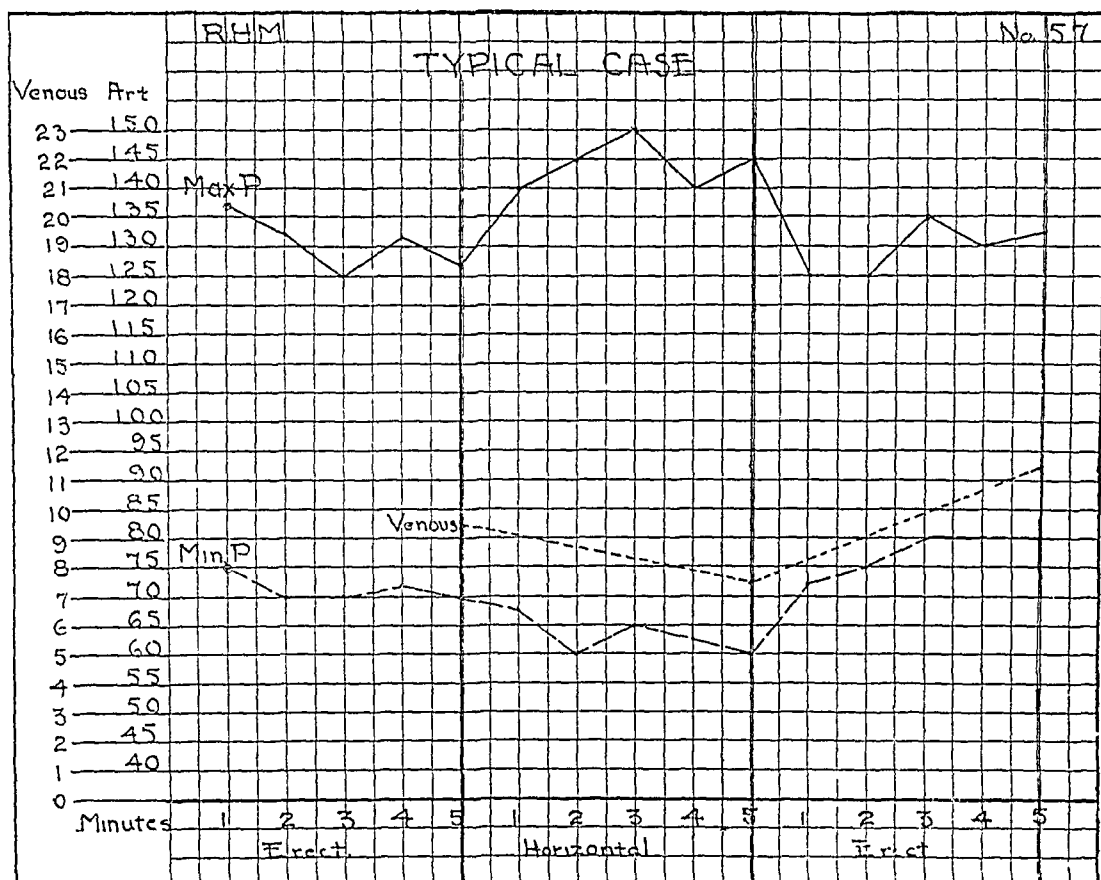


Fig 2—Chart showing maximum and minimum pulse pressure in the erect and horizontal positions in a typical case

cases and not so high as the first in five cases. The pulse pressure from erect to horizontal increased in nine, and diminished in two. From horizontal to erect, diminished in nine and increased in two. This fall was lower than the first reading in six cases.

*In the Weaker Half*—From erect to horizontal, the maximum rose in six and fell in four. From horizontal to erect, caused a fall in eight and a rise in two. This fall was lower than the first reading in the erect in eight and higher in two.

The minimum pressure on change from erect to horizontal fell in nine and rose in one. From horizontal back to the erect again, caused a

rise in all ten. In half of this ten a higher level was reached than the readings in the first erect posture; in the other half it was lower.

*In Poor Muscular Cases*—Change from erect to horizontal caused a fall in seven and a rise in six. From horizontal to erect, a fall in nine and a rise in three. In this fall eight out of eleven remained lower than the first readings in the erect posture. The minimum pressure from the erect to horizontal increased in eleven and fell in one. From horizontal back to the erect, increased in six and fell in five.

*In Heart Cases*—In this series of heart cases, we make no attempt to classify the lesions. Rather do we include those cases in which the state of the heart is frankly open to the criticism of probable cardiac inefficiency. Two cases showed irregularity, one aortic systolic murmur,

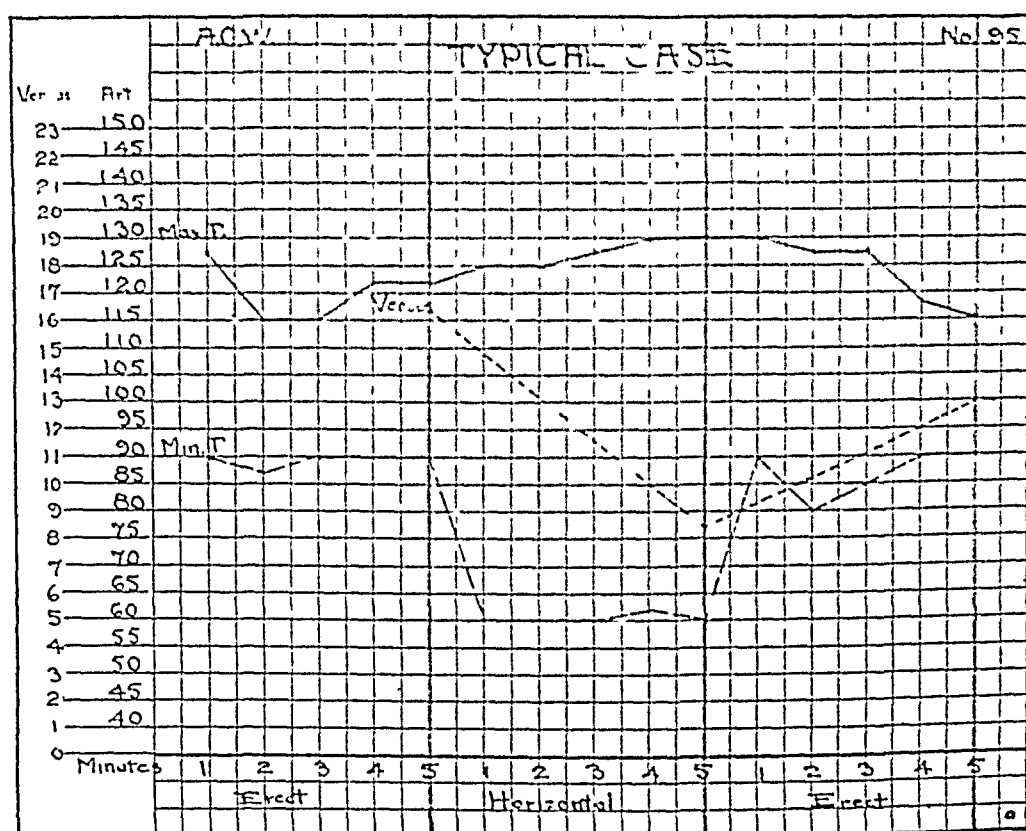


Fig 3—Chart showing maximum and minimum pulse pressure in the erect and horizontal positions in another typical case

one case Broadbent's contraction from an old pericarditis, two mitral systolic murmur cases, and two cases showed very prominent apex impact with weakness of cardiac sounds. Changing from the erect to the horizontal caused in the maximum pressure an increase in five and a fall in four. From the horizontal back to the erect, a fall in six and an increase in two. This fall was to a lower level in six out of seven cases.

The minimum pressure after change from erect to horizontal, fell in eight and rose in one. From horizontal to erect, rose in seven and fell in one. This rise was to a higher level in five out of eight cases.

### VENOUS PRESSURES

To determine first what is the height of the venous pressure in the normal, we picked out of our series of observations twenty-six cases in which we could measure the venous pressure at the level of the auricle.

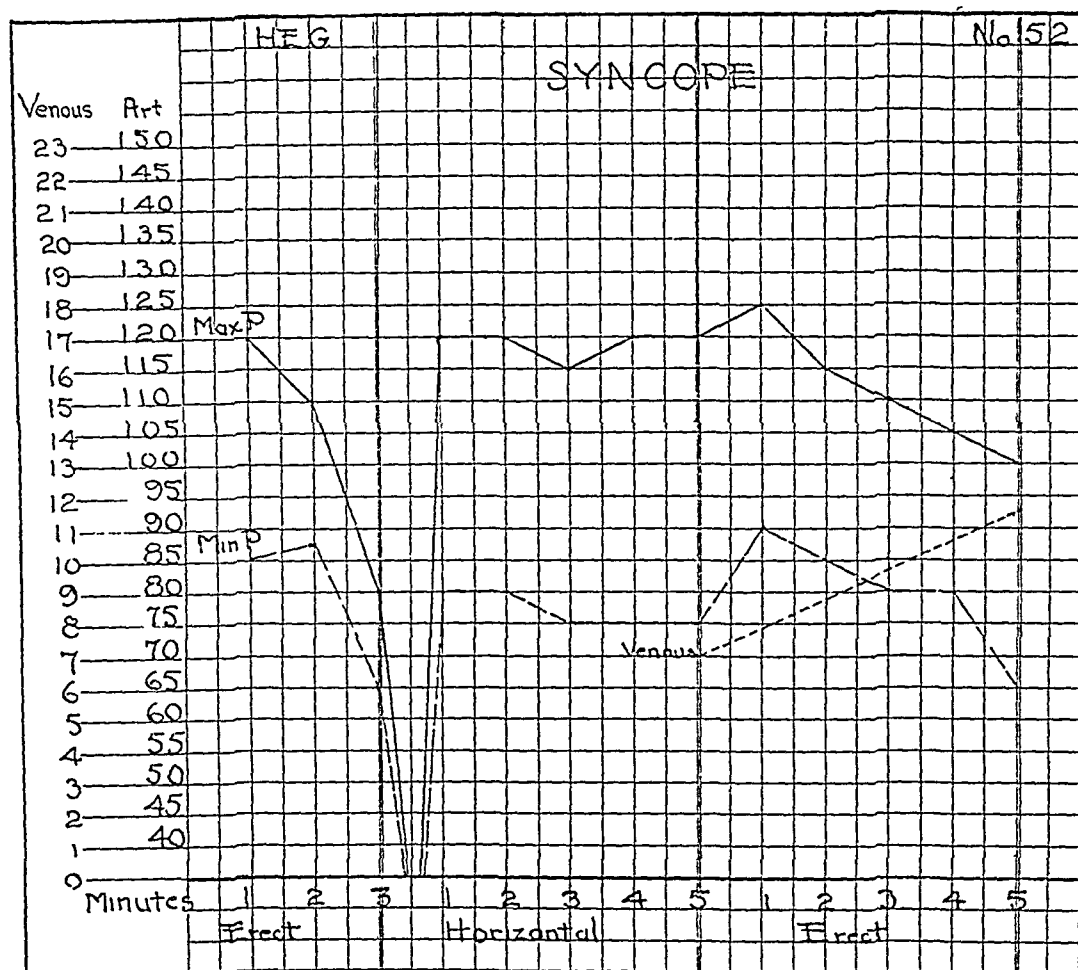


Fig 4—Chart showing syncope during the experiment with rapid rise in pulse-pressure on placing the patient in a horizontal position

In the erect posture the height varied between 8 and 18 cm water. In the horizontal between 3.5 and 11 cm. The average pressure between the ages of 16 and 20 years was 9.59 cm in the erect. Between 21 and 26 years 11.2 cm.

Change of posture in all the cases from the erect to horizontal caused a decrease in twenty-four and an increase in two. From horizontal to erect an increase in twenty-five and a decrease in one, and this increased pressure was higher than the first erect posture in twelve. It was lower in eight and equal in five.

RELATIONS BETWEEN THE PULSE PRESSURE AND VENOUS PRESSURE

In table form we arranged the cases according to the height of the pulse pressure average for five minutes. We find that the added venous pressures in the first half which includes those of the higher pulse pressure, is 127 cm water, while that of the lower pulse pressures is 123 cm. Showing that in this series the tendency is to greater pulse pressures and greater venous pressures occurring simultaneously.

RELATIONS BETWEEN "HEART CASES" AND VENOUS PRESSURE

Table 2 shows that in the case of aortic insufficiency, the venous pressure rose instead of falling on change from the erect to horizontal

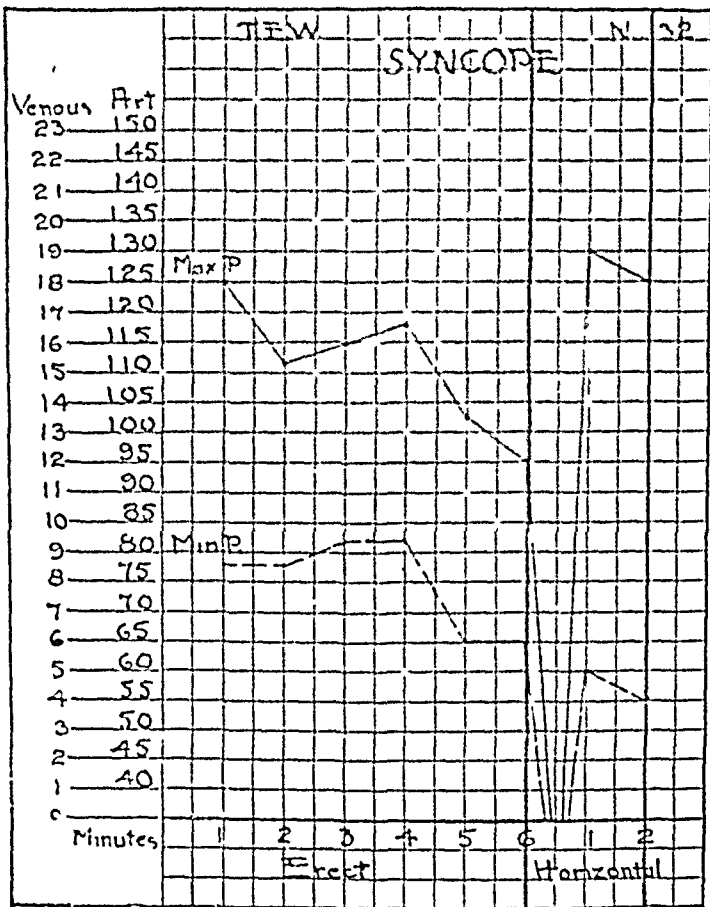


Fig 5—Chart showing rapid fall in pulse pressure during the experiment, with syncope in six minutes. Rapid rise on placing the patient in a horizontal position.

posture. The other cases, irrespective of the lesions, responded as does the normal circulation.

SYNCOPE

In a number of these cases syncope occurred during the examination. The two charts (Charts 4 and 5) show the behavior of the arterial and venous pressures.

In one case (Chart 4) the maximum pressure fell in three minutes, from 120 down to 80, the minimum from 85 to 65, then the pulse at the brachial became inaudible, and the subject soon relaxed to falling. We tilted the table to the horizontal posture and within two minutes got the first reading at which the maximum pressure had reached its former height, but the minimum pressure did not go quite so high as formerly.

After five minutes in the horizontal posture the erect posture was resumed. The maximum pressure responded normally by falling, but the minimum pressure showed a tendency to fall instead of rising as it should. The venous pressure reading from horizontal to erect responded normally.

TABLE 2—RELATIONS BETWEEN HEART CASES AND VENOUS PRESSURE

No		Erect	Horizontal	Erect
18	Aortic insufficiency	×	+	+
92	Hypertrophy—general condition poor	×	—	+
36	Mitral insufficiency	×	—	+
54	Broadbent's contraction	×	—	+
35	Irregular heart	×	—	+
90	Hypertrophy—general condition poor	×	—	+

The second case (Chart 5) showed a steady falling of pressure with each minute reading, and from the restlessness of the subject we suspected what was going to happen, therefore, we carried on our observations in the first erect posture for six minutes, at which time the sounds at the brachial became inaudible, and the subject a little later, relaxed to falling. After being placed in the horizontal posture, the maximum pressure rose higher than at the first reading in the erect, and the minimum pressure rose, but as in the other case, to not so high a level as formerly. In this case we did not get the venous readings.

## SUMMARY

1 When the element of muscular effort has been eliminated, change of bodily posture from the erect to the horizontal will cause an increase in the maximum pressure, a decrease in the minimum pressure and an increase in the pulse pressure.

2 After five minutes in the horizontal posture when the subject is retitled to the erect posture, the maximum pressure will diminish, the minimum pressure increase and the pulse pressure diminish. It will be noted that in both instances the pulse pressure follows the same trend as the maximum pressure.

3 Change of posture from the erect to horizontal caused a fall in the venous pressure.

4 Change of posture from the horizontal to erect caused an increase of the venous pressure.

It will be noted that the venous pressure follows the same trend as the minimum pressure

Nearly all subjects of this series responded in the same way. The most notable exception was in the "Poor Muscular Cases." These cases showed a tendency to a reversal of the pressure curve. From erect to horizontal caused in more than half of the cases a decrease of the maximum pressure and an increase of minimum pressure.

GENERAL SUMMARY

	Erect	Horizontal	Erect
Maximum	X	+	—
Minimum	X	—	+
Pulse pressure	X	+	—
Venous pressure	X	—	+

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# BUDDING AND OTHER FORMS IN TROPHOZOITES OF ENTAMOEBA TETRAGENA

SIMULATING THE "SPORE CYST" FORMS ATTRIBUTED TO "ENTAMOEBA  
HISTOLYTICA" ~

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ANCON, CANAL ZONE

## INTRODUCTION

Working with richly infected material from kittens infected rectally with *E. tetragena*, very interesting forms were detected in a senile race. These are so much like Hartmann's figures of Schaudinn's preparations illustrating the spore cyst development of *E. histolytica* as to be practically identical with them. They also correspond very closely with Schaudinn's<sup>1</sup> and Craig's<sup>2</sup> descriptions of the alleged perpetuating forms of *E. histolytica*.

Hartmann<sup>3</sup> has called attention to the wide-spread distribution of *E. tetragena*, and has expressed his opinion that most of Schaudinn's *histolytica* material is really *E. tetragena*.

In Panama, while the perpetuating forms of *E. tetragena* (cysts) have been detected in a number of cases, nothing save some budding forms in fresh material from one fatal case, and the remarkable forms in rectally infected kittens have ever been seen by me which resemble the descriptions of Schaudinn and Craig for the spore cyst development of *E. histolytica*.

Based on findings in clinical cases of entamebic dysentery, from autopsy material and animal feedings and inoculations, I am of the opinion that the pathogenic entameba of Panama is *E. tetragena*, and in all likelihood *E. histolytica* is a spurious species.

## FEATURES OF THE REPRODUCTIVE PROCESS IN *E. HISTOLYTICA*, ACCORDING TO SCHAUDINN

Schaudinn (quoted from Craig, *loc cit*, Note 2) stated that the reproduction of *E. histolytica* by sporulation occurs after a lengthy period of lively increase when the conditions of life have deteriorated. In dysentery this is simultaneous with the commencement of healing. During the height of the disease he never found these permanent stages.

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\* Manuscript submitted for publication in THE ARCHIVES, March 15, 1913

1 Schaudinn Arb a d k Gsndhtsamte, 1903, xiv, 3, p. 547

2 Craig Parasitic Amoebae of Man, 1911, Lippincott, Phila.

3 Hartmann Handb d Pathog Protoz (Prowazek), First Instalment  
Barth Leipzig, 1911



Schaudinn further stated that the beginning of the spore formation is first noticed in the nuclear apparatus, and the succeeding changes noted by him are as follows:

- 1 Broadening of the peripheral chromatin zone of the nucleus, and extension into the nuclear plasma, the nucleus becoming less differentiated
- 2 Large quantities of chromatin are surrendered to the cytoplasm in the form of granules
- 3 The amount of chromatin in the cytoplasm increases until the entire organism appears to be filled with it, while the remainder of the nucleus degenerates

Forms noted during life

- 1 Location of the nucleus at the periphery generally in the shape of a flat disk
- 2 Sometimes expulsion of the nucleus under the eye of the observer is seen
- 3 Development of a fine fibrous structure of the peripheral ectoplasm indicating the formation of buds which finally project from the surface
- 4 Separation of buds in the shape of small globules 3 to 7 microns in diameter
- 5 Development of a double outline membrane on the globules, which becomes brownish in color in a few hours
- 6 Breaking up of parent entameba

A staining of the series of stages gives the following results

- 1 Giving off chromidia by the nucleus to the cytoplasm, which appears to multiply and scatter through the entire organism the nucleus degenerating and either dissolving or being extruded
- 2 Withdrawal of chromidia from endoplasm and collecting in dense fibrous tissue of ectoplasm, permeating the latter as a uniform reticular chromidial mass
- 3 Ectoplasma buds filled with a chromidial mass protrude on the surface of the parasite and are budded off from the parent body
- 4 When the sheath of these globules is formed, staining substances no longer set well

#### THE ENTAMEBA USED IN THESE EXPERIMENTS

Recently I received some material from a case of entamebic dysentery in an American. The stool contained mucus, pus, blood and entamebae. The trophozoites were large in size, some were vacuolated and others granular. The nucleus of many was distinctly visible in the fresh specimen and many of the trophozoites had engulfed erythrocytes. In wet-fixed preparations stained with Mallory's phosphotungstic acid hematoxylin, differentiated with permanganate of potash, the centriole and peripheral chromatin granules were of fair size and stained sharply. The karyosome was usually indistinct, though definite in a few forms. No cysts were seen and none of the trophozoites contained chromidia. On the whole, most of the trophozoites were of the adolescent or histolytica type, meaning by this that they resembled the forms figured by Hartmann and Werner as *E. histolytica* in contradistinction to the forms of the mature smaller generation with prominent karyosomes and large blocks of chromidia usually recognized as *E. tetragena*.

## METHOD OF MATURING THE STRAIN

Kittens were inoculated by rectum with material from this case and when the disease developed and the kittens died, another set was inoculated rectally with material from the preceding and so on, in order to mature the strain. As the strain matured, the trophozoites became reduced in size, their karyosomes and centrioles more conspicuous, and chromidia began to appear first as fine acicular particles in the third remove, and later in the fourth remove as small and large blocks. From the fourth remove a number of stained preparations wet and dry-fixed were made. An examination of these preparations showed that the trophozoites had now become reduced in size and chromidia had appeared in every trophozoite, though entirely absent in the first and second removes, and the karyosome of the nucleus had usually become very prominent, not only so, but unmistakable uninuclear cysts were seen in this material from the fourth remove.

THE ABERRANT FORMS OF *E. TETRAGENA* SIMULATING THE "SPORE CYST"  
DEVELOPMENT OF "*E. HISTOLYTICA*"

Dry-fixed films were examined, these had been stained with Hasting's stain, followed by Giemsa's, and differentiated with ammoniated 60 per cent alcohol. In certain slides most of the trophozoites contained chromidia. The cytoplasm was frequently condensed along the periphery, and also here and there in quite solid islands staining like the chromidia a deep navy blue. In other trophozoites the paler blue endoplasm or the dark blue condensed periphery, sometimes containing chromidia, had become pinched off into buds and protuberances of irregular size. These in a number of instances had become detached from the parent body. The buds never contained purple-staining substance save when a bud corresponded with a nucleus or when it was obscured by what appeared to be superimposed bacteria or debris. Most of the dry fixed films did not present the budding appearances just described, but displayed a more homogeneous appearance free from the condensed cytoplasm at the periphery, and budding forms were not detected. A number of trophozoites contained nuclear fragments of tissue cells or leukocytes. In contradistinction to chromidia, which stains navy blue, these nuclear fragments stained purple exactly like tissue nuclei outside nearby. This is a point of some importance, for these nuclear fragments no doubt have been mistaken for chromidia, which does not stain purple with Romanowsky stains, but navy blue.

A number of wet-fixed films, however, contained the peculiar forms in question. These were fixed in Zenker's solution one-eighth, one-fourth and one-half strengths, and in Schaudinn's fluid, besides various other fixatives, in order that comparisons might be made of the effects of

various fluids on the entameba. Likewise, different staining methods were employed. Good results were obtained with Mallory's phosphotungstic hematoxylin and Leishman's alkaline methylene blue (polychrome), differentiated with tannin. All the preparations presented unmistakable and positive evidences of their identity, i. e. *L. tetragena*, by the nuclear characteristics, chromidia and the presence of cysts. The apparently normal trophozoites were present in enormous numbers; many fields contained nothing but them. The vast majority of the forms were typical trophozoites of the mature or pre-cyst generation of *L. tetragena*. The nucleus stained sharply, there was a densely stained large centriole and usually a conspicuous karyosome. The chromidia present was in large or small crystalloid particles. These trophozoites had in general the appearance of *L. minuta* Elmassian and of *L. tetragena*, as figured by Hartmann, Viereck, Weiner and Craig.

The nucleus in the aberrant forms usually took up an extreme peripheral position, often as though stuck on the outside of the trophozoite. Frequently the nucleus was attached to the trophozoite by a long or short thin pedicle, and a number of free nuclei were seen. The nucleus in these aberrant forms rarely stained sharply, the peripheral chromatin being diffused, swollen and not displaying the granules noted in normal tetragena trophozoites nearby. The nucleoplasm was stained rather deeply, as though due to diffused chromatin in the plasma. There was marked distortion of the nucleus in a few forms, it having taken on an ameboid shape. The centriole usually stained well, but the karyosome, while occasionally to be made out in part, was usually very indistinct and obscured by the diffused chromatin in the nucleoplasm. In some of the budding forms the nucleus failed entirely to stain, but its architecture sometimes could still be made out distinctly. The cytoplasm of some of the aberrant forms stained deeply around the nuclear area as though chromatin was being diffused out in a fluid form from the nucleus. Occasionally one found a trophozoite free from chromidia or in the act of extruding it, and a good deal of free chromidia was seen in the films. These trophozoites which were more or less free from chromidia had a clear translucent appearance, being free from chromidia, and these were the ones that exhibited budding forms. The buds appeared anywhere on the periphery and in numbers from one or two to a dozen. They were usually translucent and homogeneous, and while most were free from chromidia, some of them contained particles of chromidia, or oftener a pinched-up chromidial mass usually attached to the periphery of the bud. The budding forms always stained like defunct microorganisms.

Comparing the pictures displayed in wet-fixed preparations with those dry-fixed and stained with Romanowsky, it is noted that budding forms, extruded buds, chromidia and nuclei are seen in each.

Naked protoplasmic buds, excepting in the case of the nucleus, are usually free from chromidia or chromatin, and nothing like a bud capsule was seen. The extreme dislocation of the nucleus, as well as its presence attached by a pedicle, is noted in each. A very striking feature of the dry-fixed film is the pallor or peculiar greenish blue-staining ground substance or karyoplasm which supports the purple-staining substance (karyosome) of the nucleus. This pallor and absence of dark blue-staining substance may correspond with the diffusion of the basichromatin out from the nucleus noted in some of the wet-fixed films.

#### SCHAUDINN'S ERRONEOUS INTERPRETATIONS

Schaudinn accurately described the changes noted by him in his Chinese case of dysentery, and his descriptions and Hartmann's drawings of Schaudinn's preparations of *E. histolytica* correspond precisely with changes here described in a race of *E. tetragena* from man, matured in the kitten. I believe, however, that Schaudinn's interpretations were entirely wrong in so far as they referred to a mode of development.

Seriatim the points of correspondence and difference between Schaudinn's observations in man and my findings in kittens are these, the numbers referring to paragraphs in Schaudinn's propositions:

1. There is, as Schaudinn described, a broadening of the peripheral chromatin zone of the nucleus and its extension into the nuclear plasm. The nucleus becomes less sharply differentiated and chromatin appears to be distributed to the cytoplasm, but chiefly, I believe, by diffusion of fluid and not usually in the form of granules.

2 and 3. The chromidia seen in the cytoplasm of the trophozoites, in my opinion, would seem to be chromidia more nearly in the sense of Hertwig, that is, extranuclear chromatin, though not functionless. This chromidia, I believe, is formed as fine particles in the cytoplasm and is trophochromidia in the sense of Mesnil '05. Dry-fixed preparations stained with Romanowsky show that this chromidia is formed in the cytoplasm, and as the strain increases in age, the chromidia usually condenses in the form of crystal-like particles and large blocks. Traces of this chromidia were seen in Remove 3 as fine acicular navy-blue particles (Romanowsky); these become condensed to form the large-sized particles seen in Remove 4. Staining reactions seem to indicate that while there is great similarity between nuclear chromatin and trophochromidia, there are well-marked differences which may be brought out by certain stains.

#### Forms noted during life.

1. Dislocation of the nucleus. The nucleus is placed at the extreme periphery in the shape of flat disks at the border of the cytoplasm just as Schaudinn described. There is also expulsion (2) of the nucleus.

## EXPLANATION OF FIGURES

## PLATE I

Nos 1 to 12 dry fixed films, stained by Hasting's and Giemsa's stain, differentiated in ammoniated alcohol. Nos 1 to 8 show budding forms. The periphery is generally dark and the interior pale in tone. Nos 1 and 2 contain dark navy blue, almost black, crystalloidal particles of chromidia. The purple staining substance of the nucleus is imbedded in a pale blue ground substance. Dislocation of the nucleus is seen in No 6. No 5 is a trophozoite which has extruded its nucleus. Nos 9 and 10 represent a free bud of ectoplasm, and a nucleus respectively. No 11, a trophozoite with buds and five phagocytosed fragments of nuclei of tissue cells or mononuclear leukocytes. No 12, a, b and c, free tissue cell nucleus and fragments of same for comparison with phagocytosed fragments in No 11.



1



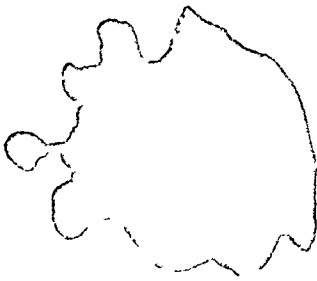
2



3



4



5



6



10



9



8



7



c  
b  
a



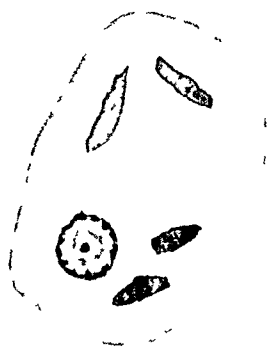
12



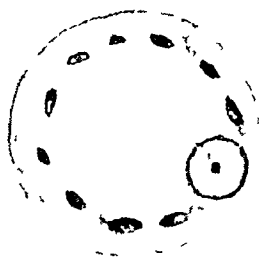
11

## PLATE II

Nos. 13 to 23 wet fixed films. No. 13 a trophozoite with typical tetragena nucleus and chromidia. This represents the vast majority of trophozoites in the films. Their outlines were round, ovoid and oblong. No. 14 a mononuclear tetragena cyst from one of the films. No. 15, dislocation of nucleus and chromidia in small particles with a large bud. No. 16 extrusion of nucleus and a bud containing a mass of chromidia. No. 17 karyorrhexis. The nucleus is apparently giving up its chromatin to the cytoplasm. Note that the tetragena features of its karyosome are still present. Two buds are shown. No. 18, dislocation of nucleus, several small buds of irregular size and one large deeply staining bud are shown. The trophozoite still contains a few particles of chromidia. No. 19, dislocation of nucleus, streams of chromidial (not chromatin) particles of small size concentrated along the periphery are seen. The nucleus does not stain sharply and it has parted with some of its chromatin (not chromidia) which stains the cytoplasm nearby. No. 20, a trophozoite with four small buds, chromidia and a degenerating nucleus showing karyolysis. No. 21 a trophozoite, with dislocated nucleus and many buds. It has extruded all its chromidia. No. 22, an extruded nucleus not staining sharply, the peripheral chromatin granules being indistinct and the karyosome invisible. No. 23 a trophozoite containing chromidia and several buds. The dislocated nucleus is attached to the parent body by a slender pedicle and does not stain sharply.



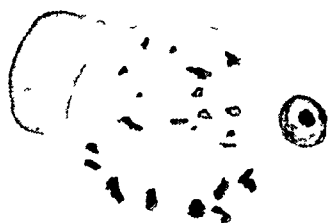
13



14



21



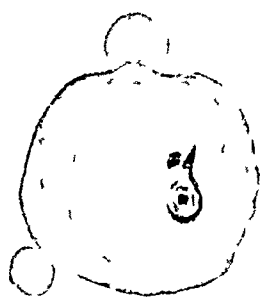
15



16



22



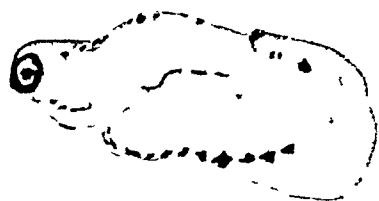
17



18



23



19



20





PLATE III

No 24, a microphotograph showing three trophozoites stuck together. The nucleus is indicated (n) as well as buds (b). The nucleus is dislocated.

3 The development of a fine fibrous structure of peripheral ectoplasm I have seen something that would probably correspond with this, though the observation was made on trophozoites from Remove 3, in which there was no budding, and the phenomenon was only observed in films fixed by Merkel's fluid Zenker's, Flemming's and Schaudinn's preparations did not show it

4 Buds are separated in the form of small globules 3 to 7  $\pm$  microns in diameter

5 The development of double-outline membranes on extruded globules was not observed Considering the pathological nature of the other related changes in the trophozoites, it would be interesting to know just what Schaudinn was observing, for in dry-fixed films stained by Romanowsky the free buds and extruded nuclei stain exactly like the nucleus and cytoplasm of the trophozoites

6 Breaking up of the parent entameba was observed

#### Stained Series.

1 My observations on the trophozoites of *E tetragena* confirm me in the opinion that chromidia is not given off by the nucleus, but is formed in the cytoplasm Chromatin, however, in these pathological forms does diffuse out in fluid form from the nucleus into the cytoplasm The nucleus does degenerate and is extruded

2 In some trophozoites chromidia was present in rather small particles and collected in reticular masses in the ectoplasm, as Schaudinn described

3 Ectoplasma buds filled with a chromidial mass were seen apparently pinched off of the parent body

4 The free globules, while detected with more difficulty in wet-fixed preparations, were seen very well in dry-fixed Romanowsky preparations Nothing like a sheath was seen, for the buds stained either navy blue or light blue like the cytoplasm of the parent entameba When an extruded nucleus was encountered it always stained like one.

#### CONCLUSION

I have seen in fresh preparations of *E tetragena* from a fatal case of dysentery bizarre pseudopodia and buds with refractile bodies in the extremities, though I did not observe extrusion of buds or nuclei If one had merely observed in fresh preparations alone from a case of dysentery in man, the changes corresponding to those seen in stained preparations, the impression received would no doubt have been very much like that described by Schaudinn and Craig as the spore cyst formation of *E histolytica*, but from an examination of the far more richly infected material from the kitten "which occurs after a lengthy period of lively

increase,' the true nature of the budding forms is understood and the opinion is formed that these changes are analogous to such essentially pathological manifestations of cellular degeneration as karyolysis, karyorrhexis, pyknosis and dislocation and extrusion of nuclei, moreover, the budding process is analogous to changes seen in mononuclear metazoal cells, for example, in defunct plasma cells or lymphocytes in the bloodstream, lymph-nodes and other locations

The descriptions of the life cycle of *E. histolytica* by Schaudinn and Craig, therefore, are in all likelihood those of a spurious species, having resulted from observations of pathological changes in senile races of *E. tetragena*

Board of Health Laboratories

# ACTIVE HYPEREMIA FOLLOWING LOCAL EXPOSURE TO COLD

A W HEWLETT, M D

ANN ARBOR

It is well known that thermic stimuli exert a powerful influence on the local blood-vessels. In our experience, the application of cold water has invariably slowed the current of blood through the arm and this has been commonly followed by some constriction of the vessels even after the temperature of the water has been raised,<sup>1</sup> or after the arm has been withdrawn from the cold water. In the patient, whose history follows, a marked vascular dilatation followed the exposure of the arm to moderately cold water. This phenomenon, which was evidently associated with the symptoms present in this patient, is unusual if not pathological. It is related on the one hand to milder degrees of frost-bite and chilblain, and on the other to a disturbed vasomotor control at the surface of the body.

*History*—Mr E C, 19 years old, entered the University Hospital Nov 20, 1912, complaining of itching, burning and swelling over various parts of the body after these had been exposed to cold. The family and past history were unimportant. The present trouble was first noticed with the onset of cold weather two years ago. Shortly after the patient is exposed to cold, the exposed portions of the body become white and numb. As the result of prolonged exposure, but more especially after coming into a warm room following exposure, the parts exposed become red and swollen and the patient suffers from burning and itching sensations in the exposed areas. At times the swelling of the hand is so considerable as to interfere with the movement of the fingers. His eyes have been partially closed after facing a cold wind. The buttocks have shown similar phenomena after sitting on a cold seat, and the forearm after a cold iron has lain across it. Even the tongue and throat are said to have become swollen after eating ice cream. These phenomena have troubled him only during the winter. One year ago they were so severe that he was compelled to leave school. Aside from these symptoms he is in good health and has gained twenty pounds in weight during the past two years.

*Physical Examination*—Physical examination showed a young man of normal appearance. A few râles, probably due to bronchitis, were heard over the lungs. The heart showed systolic murmurs at the apex and base, which were probably of an accidental character. The hands were slightly cyanotic and perspired easily. Well marked dermatographia with tendency to wheal formation could be elicited by mechanical stimulation of the skin. The laboratory findings were practically negative. The blood coagulated in two and three-fourths to four minutes.

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<sup>1</sup> Manuscript presented for publication Feb 7, 1913.

<sup>\*</sup> From the Department of Internal Medicine, University of Michigan.

1 Hewlett, A W, Van Zwaluwenburg, J G, and Marshall, M. The Effect of Some Hydrotherapeutic Procedures on the Blood-Flow in the Arm. THE ARCHIVES INT MED, 1911 VIII, 591.

The blood-flow through the arms was studied while the symptoms complained of by the patient were reproduced by exposures to cold water. Although but three experiments of this type could be performed and these left certain points undecided, nevertheless, the results indicated that in this patient an unusual vascular reaction followed exposure to cold water.

*Experiment 1*—In the first experiment the patient, stripped to the waist, was placed in a warm room and the room was later cooled by opening the windows. The right arm was exposed to air only. After a few preliminary determinations, the left was surrounded by cold water which was maintained at a temperature averaging  $19\frac{1}{2}$  C for nearly an hour. At the end of this time, the arm was taken out of the cold water, the plethysmograph was emptied and the dried arm thrust back into the apparatus for further determinations of the blood flow. The results of this experiment are shown in Table 1.

TABLE 1—EXPERIMENT 1 SHOWING EFFECT ON BLOOD FLOW OF IMMERSION OF ARM IN COLD WATER

Time	Room Temp, (	Temp of water about left arm, C	Flow in left arm, cc	Flow in right arm, cc	Remarks
9 55	27 $\frac{1}{2}$		12.0	10.0	Patient quite warm
10 00			9.6		
10 05	27 $\frac{1}{2}$		10.4	10.6	
10 15					Cold water placed about left arm
10 30	27	23 $\frac{1}{2}$	1.0	6.3	
10 40	27	19	5.3	1.3	
10 45	27	18 $\frac{1}{4}$	1.2	3.9	
10 55	27	19 $\frac{1}{2}$	3.2	3.6	
11 10	24	19 $\frac{1}{2}$	4.2	3.6	
11 30	22	20	3.0		Patient feels cold
11 35					Left hand dried. At first arm was slightly cyanotic. Later bright red and warm. Some burning and itching.
11 45	23	20	10.0	2.0	
12 00	23		7.2	1.8	Left hand slightly swollen. Burning and itching passing off.

It will be seen that at the beginning of the experiment the blood-flow was unusually rapid in both arms, owing doubtless to the effect of being for some time in the warm room. When the left arm was covered with cold water, the blood-flow in both arms dropped rather suddenly and the rate of flow continued to lessen during the period of exposure, owing in part to the cooling of the room, in part perhaps to the cold water. When the left arm was taken out of the cold water the skin became bright red, and after drying it felt quite warm. The hand became slightly swollen. After drying, the blood-flow in the arm exposed to the cold water showed decided acceleration, while the flow in the opposite arm continued to lessen.

*Experiment 2*—The second experiment was performed in a warm room, the patient being very warm throughout. The right arm was thrust into ice water, until pain was caused. It was then taken out and thrust in again. This intermittent exposure was continued for half an hour. Following this the rate was determined in both arms. The left showed a rate of 15 cc per 100 cc of arm substance per minute, and the right, a rate of 12.5 cc to cold. The failure to reproduce the vascular phenomena in this experiment may have been due either to the warm room which caused the blood-flow in the arms to be very rapid and so prevented cooling the tissues, or it may have been due to the intermittent character of the exposure.

*Experiment 3*—In the third experiment, the room was maintained at a constant temperature of 21 C, which produced a feeling of slight chilliness in the partially clad patient. The right arm was soaked continuously in water at 16 C for a period of twenty minutes. During this time, the arm became reddened and slightly cyanotic and after withdrawal from the water it felt warm and itched considerably. Some time later it became distinctly swollen. After the exposure, the exposed arm showed a blood-flow of 9.4 cc per 100 cc of arm substance, while the other showed a blood-flow of 17 cc. Somewhat later, the former showed 8.5 cc and the latter 18 cc.

TABLE 2—EXPERIMENT 3, RESULTS OF IMMERSION OF ARM IN WATER AT 16 C

Time	Room Temp, C	Temp of water about right arm, C	Flow in left arm, cc	Flow in right arm, cc	Remarks
3 10	21	16			Right arm in water, patient slightly chilly
3 30					Right arm out of water
3 40	20		17	9.4	Right arm reddened
3 50	20			6.0	
4 00	19		18	8.5	Right hand is swollen

To recapitulate. A young patient who showed sweating hands and dermatographia entered the hospital on account of itching and burning sensations, which followed exposures to moderate cold. These symptoms, which could be reproduced by exposure to cold water, were associated with a definite increase in blood-flow of the arm so exposed relative to the blood-flow in the other arm. The condition corresponded to the milder degrees of frost-bite, which are often followed by erythema and slight edema, and are described as a form of chilblain. The circumscribed, reddish and edematous areas often met with in the latter condition were, however, absent in our patient. Furthermore, the condition was peculiar in that it was induced by relatively slight cold, and in its localizations on such unusual sites as the forearm, buttocks and mouth. As an unusual vasomotor reflex, the condition might be grouped in the broad category of the vasomotor ataxias described by Solis-Cohen.

That the reaction was indeed unusual might be inferred from our earlier experiments,<sup>1</sup> in which, after cooling the arm, the temperature of the surrounding water was again raised, and slower rather than faster rates of flow were obtained for given temperatures of the surrounding water. It seemed advisable, however, to duplicate the above experiments on other individuals. As the following tables show, no secondary dilata-

tion of the blood-vessels occurred in these individuals after exposures to fairly cold water for half an hour or so. Instead the arms exposed remained unusually cold and pale for some time and the blood-flow remained exceedingly slow.

TABLE 3—EXPERIMENT 4, EFFECT ON BLOOD FLOW IN NORMAL INDIVIDUAL OF IMMERSION OF ARM IN COLD WATER

Time	Room Temp., C	Temp of water about left arm, C	Flow in left arm, cc	Flow in right arm, cc	Remarks
3 05	21.5		56	53	
3 10	21.5		45	46	
3 12			.		Water placed about left arm
3 15	21.0	24	36	38	
3 25	21.0	22	35	43	Left arm fairly cold
3 45	21.5	17	20	37	
4 00	21.5	18	23	31	
4 02					Water out Dried Arm cold
4 10	21.5		21	32	
4 12			15		
4 20	21.5		17	54	Left arm still cold

TABLE 4—EXPERIMENT 5, EFFECT OF COLD ON BLOOD FLOW IN NORMAL INDIVIDUAL

Time	Room Temp., C	Temp of water about left arm C	Flow in left arm, cc	Flow in right arm, cc	Remarks
10 40	Cool		29	30	
10 45					Water placed about left arm
10 55		21	185	31	
11 05		17	39	30	
11 20		16	27	27	
11 35		16	22	24	
11 40					Water out
11 50			15	19	
12 00			14	22	

TABLE 5—EXPERIMENT 6, EFFECT OF COLD ON BLOOD FLOW IN NORMAL INDIVIDUAL

Time	Room Temp., C	Temp of water about left arm, C	Flow in left arm, cc	Flow in right arm, cc	Remarks
3 30	24		40	40	
3 25					Water placed about left arm
3 42	24	19.5	20	32	
3 50	24	19.5		31	
4 00	24	18.0	17	50	
4 10	24	17.0	20	50	
4 13	24		20	45	Water out Arm cold and pale
4 20	24		20	45	
4 25	24		20	60	

From Experiment 1, it was evident that the abnormal hyperemia following cold did not depend primarily on a previously slow rate of blood-flow, for the flow was equally reduced in the other arm, and yet

there was no reactive hyperemia. It probably depended on a local cooling of the vascular mechanism, being in this way directly related to the condition which prevails in frost-bite. The development of edema also indicated a direct action of the cold on the blood-vessels.

Nor were the symptoms during the reactive hyperemia readily explainable on the simple assumption of an increased blood-flow to the arm, for equally fast or faster rates were encountered in Experiments 1 and 2 without the characteristic symptoms of burning, itching and swelling. It may be, however, that the skin circulation, as distinguished from that of the deeper arm structures, was markedly increased during the reactive stage, a supposition supported by the intense redness of the skin. This is what one would expect if, as we believe, the condition depended primarily on a reduction in the temperature of the superficial tissues.

#### CONCLUSIONS

1 In most individuals a diminished blood-flow accompanies and follows the prolonged action of moderately cold water on the arm.

2 An active hyperemia following exposures to moderate cold is described in a patient showing other signs of cutaneous vasomotor instability. The condition present probably corresponded to the milder stages of ordinary frost-bite, or chilblain, but in our patient it occurred more readily than normal and also in unusual locations. It represented an unusual vasomotor response to moderate cold.

3 The reaction was probably due to the direct effect of the cold on the cutaneous or subcutaneous vascular mechanism.



## A MODIFIED WASSERMANN \*

LOYD OSCAR THOMPSON, M.D.

HITTI ROCK

There are several undesirable features in the original Wassermann technic of the complement fixation test for syphilis as well as in the Noguchi modification some of which may be sources of error.

In the original Wassermann technic the presence of variable amount of natural antishoop antioepto, which is found in all human sera may lead to error, unless removed by the tedious method of bringing in contact with sheep cells. Another objection to the original Wassermann is that unless a sheep is kept in the animal rooms of the laboratory it is sometimes difficult to secure corpuscles for the test, while the keeping of a sheep is more or less expensive, and in some laboratories well nigh impossible.

In the Noguchi technic the use of a non-inactivated serum might theoretically, be a source of error, although practically, owing to the small amount of serum used, probably is not. But the use of the small quantity of serum (0.2 cc) undoubtedly sometimes leads to error, from the fact that such a small quantity might, in very light cases of luetic infection, not contain a sufficient number of antibodies to cause a binding of complement. Further, the use of non-specific antigen is open to objection. While it is not now thought that the Wassermann is a true antigen-antibody reaction, it is conceded by the majority of workers that the specificity of the antigen undoubtedly plays an important rôle in some cases.

Another objection to the Noguchi technic is that in dealing with such small quantities of the reagents as are used accuracy is difficult. This is especially true in the dose of the patient's serum, for which Noguchi recommends one drop from a capillary pipet. This is inaccurate and unscientific. Further the total volume in each tube being only one cubic centimeter the reaction is not as clear cut as when a greater volume is used.

Recently Jobling<sup>1</sup> has advocated the use of a hen hemolytic system. I have not used this system, and can see no reason for so doing. It is open to practically the same objection as the sheep system, viz, the necessity of keeping chickens in the laboratory, and that all human sera

\* From the Laboratory of Clinical Diagnosis, Medical Department, University of Arkansas.

\* Manuscript submitted for publication in THE ARCHIVES March 15, 1913.

1 Personal communication.

contain a variable amount of normal antihemagglutinating serum. And further, as the red corpuscles of the hen are nucleated, a greater precipitate will be formed than with the non-nucleated corpuscles.

For some time past in my serological work with syphilis, I have been using a modification of the Wassermann which partakes somewhat of the original technique and also of the Noguchi method.

#### AMBOCEPTOR

Antihuman amboceptor is used. Large healthy rabbits (Belgian hares are preferred) are injected either intraperitoneally or intravenously with thoroughly washed human corpuscles. Different workers have advocated different methods of injecting. I have obtained the highest titer by injecting intravenously 2, 4, 4, 5 and 6 c.c. four days apart and bleeding nine days after the last injection. I do not kill the rabbit, but bleed from the heart with a large glass syringe (A 25 c.c. Burioughs-Wellcome or Luer with a 20-gauge needle is very satisfactory). Twenty to 30 c.c. of blood may be drawn with perfect safety, and the rabbit may be kept for future use. The amboceptor serum is preserved with a 0.5 per cent phenol (best obtained by adding one part of a 5 per cent phenol solution to nine parts of serum); in small glass-stoppered bottles and stored in the ice-box. It may be kept this way for months without losing its strength.

Amboceptor may be kept as advocated by Noguchi<sup>2</sup> dried on filter paper. I have not found this to be of any advantage. In fact, it has the decided disadvantage of requiring much more work, of the serum not always being evenly distributed on the paper, thus causing error, and of not giving quite as clear cut a reaction on account of the paper being in the tube. H. A. Thompson<sup>3</sup> has overcome these last two objections by soaking the paper in salt solution in the incubator for a few hours before performing a test, discarding the paper and using the solution.

#### COMPLEMENT

Ten per cent solution of fresh guinea-pig serum is used for complement. I wish to emphasize the fact that it is absolutely unnecessary to sacrifice a pig every time a few tests are made. From 5 to 10 c.c. of blood may be withdrawn from the heart with perfect safety. The blood is drawn just prior to performing the test, placed in a centrifuge tube and the serum separated immediately by centrifugalization. It has been stated<sup>4</sup> that serum so secured does not show as high complement value as if allowed to stand in the ice-box over night. I have not found this to

<sup>2</sup> Noguchi, H. The Serum Diagnosis of Syphilis. Phila. 1911.

<sup>3</sup> Personal communication.

<sup>4</sup> Miller, Florence W. Noguchi Technique. Interstate Med. Jour., February, 1913.

be the case. In fact, I have sometimes secured a complement with a higher titer by immediate centrifugalization than I have by allowing the blood to stand.

#### ANTIGEN

Alcoholic extract of liver from a syphilitic fetus is used.

#### PATIENT'S SERUM

I cannot agree with those who advocate the securing of the patient's serum by pricking the ear or finger and "milking" the blood into a tube, except in the case of young children and very fleshy adults. It is much easier, quicker and less painful to draw a sufficient quantity (3 to 5 cc) from one of the veins of the elbow with a syringe. In my private practice when a patient comes to the laboratory the blood is immediately centrifugalized, the serum pipetted off and stored in the ice-box till used. Otherwise, the blood is allowed to clot and the serum collected in the usual way. One-tenth of a cubic centimeter of serum is used, which is inactivated for thirty minutes at 55 to 56 centigrade.

#### CORPUSCLE SUSPENSION

Five-tenths of a cubic centimeter of a 5 per cent solution of human corpuscles in 0.9 per cent sodium chlorid solution is used. The corpuscles may be secured from the patient, from the worker himself or from any other individual. It is my custom to place about 10 cc of sodium citrate solution (2 per cent sodium citrate in 0.9 per cent sodium chlorid solution) in a centrifuge tube, and when a test is to be performed to add about 1 cc of the blood from the patient. The remainder, 3 or 4 cc, being used for the test as described above. The sodium citrate prevents clotting, and on centrifugalization the corpuscles are thrown to the bottom of the tube. They are washed twice more in normal salt solution and a 5 per cent solution made.

#### TITRATION OF REAGENTS

Before the actual performing of the test the various reagents must be titrated, that is, the strength of the amboceptor, antigen and complement must be so determined. The dosage of the patient's serum (0.1 cc), is chosen as being the smallest amount sure to contain sufficient antibodies to bind complement if any are present.

The dosage of corpuscle suspension (0.5 cc) makes a 1 per cent solution when the total volume in the tube is brought up to 2.5 cc, and this has been found to give the clearest reaction.

In titrating the amboceptor and complement two sets of tubes are used. To each tube of one set is added 0.1 cc of inactivated patient's serum, and to each tube of the other set one unit of antigen is added, as

frequently the titer is higher without them. It is not necessary to titrate the antigen and amboceptor each time, as they are fairly stable, but complement should invariably be titrated before each test.

#### PERFORMING OF THE TEST

The actual performing of the test is carried out as follows:

A test-tube rack made of galvanized iron with three rows of holes is used. Three tubes are used for each serum to be tested, three for the negative control serum, and three for the positive control serum. In addition to these, eight tubes to control the reagents are used.

The three tubes for the serums to be tested and the control sera are placed opposite one another in the three rows of holes in the rack. One-tenth of a cubic centimeter of serum is put into each tube and the rack placed in the water bath at 55 to 56 centigrade for one-half hour. Only the amount of serum required for the test is inactivated at one time. This is done so that when a strongly positive serum is found the remaining amount may be preserved. It has been found that non-inactivated serums retain their antibodies much longer than do inactivated sera.

TABLE 1—TUBES FOR TEST

Tube	Serum	Complement, Units	Antigen	Amboceptor, Units	Corpuscles c c	NaCl q s c c	Result
Rear	0.1	2	0	2	0.5	2.5	Hem.
Center	0.1	0	0	2	0.5	2.5	No Hem.
Front	0.1	2	1 unit	2	0.5	2.5	Hem. or no Hem.

After inactivation the tubes are cooled, two units of complement placed in each tube of the front and rear rows, and one unit of antigen placed in each tube of the front row. With normal salt solution the volume in the tubes is then brought up to 2.5 c c, less 0.5 c c for the corpuscle suspension and the amount of two amboceptor units. The rack is then placed in the water bath at 37.5 centigrade for one-half hour. Following this first incubation, two units of amboceptor and 0.5 c c of corpuscle suspension are added to all the tubes. Incubation is then continued for one hour, during which time the tubes should be shaken every fifteen or twenty minutes to facilitate hemolysis. It will be seen that in the rear tubes which contain no antigen there should be complete hemolysis, and in the center tubes, which contain no complement, there should be no hemolysis. And in the front tubes there should or should not be hemolysis, depending on whether the serum was positive or negative. After removing from the water bath the rack is placed in the ice-box four or five hours when the results are read.

The eight control tubes are prepared as follows. No. 1 contains complement, amboceptor and corpuscles. No. 2 complement, antigen, ambo-

ceptor and corpuscles, No. 3, complement antigen and corpuscles, No. 4, complement and corpuscles, No. 5 antigen, amboceptor and corpuscles, No. 6, antigen and corpuscles, No. 7, amboceptor and corpuscles, and No. 8, corpuscles alone. The control tubes are prepared in the same manner as the tubes for the tests, that is, the reagents are added in the same order, complement and antigen before the first incubation and amboceptor and corpuscles after. To each is added before the first incubation sufficient normal salt solution to make the total volume 2.5 cc. It will be seen from the accompanying table (Table 2), that in Tubes 1 and 2 there should be complete hemolysis, and in the remaining tubes there should be complete absence of hemolysis.

TABLE 2—CONTROL TUBES

Tube	Serum	Complement, Units	Antigen	Amboceptor, Units	Corpuscles, cc	NaCl q. cc	Result
1	0	2	0	2	0.5	2.5	Hem
2	0	2	1 unit	2	0.5	2.5	Hem
3	0	2	1 unit	0	0.5	2.5	No Hem
4	0	2	0	0	0.5	2.5	No Hem
5	0	0	1 unit	2	0.5	2.5	No Hem
6	0	0	1 unit	0	0.5	2.5	No Hem
7	0	0	0	2	0.5	2.5	No Hem
8	0	0	0	0	0.5	2.5	No Hem

## ADVANTAGES

The advantages of my system are

- 1 It does away with the chance for error which is found in the original Wassermann of the serum to be tested containing natural anti-sheep amboceptor
- 2 The ease with which the corpuscles may be secured for the test
- 3 It uses a sufficient quantity of serum to assure plenty of antibodies if any are present
- 4 The total volume in the tubes is great enough to give a clear-cut reaction
- 5 The elaborate system of controls makes an error impossible

## DISADVANTAGES

The disadvantages of my system are

- 1 The tubes must be shaken during incubation
- 2 A greater number of tubes are required

Uihuhart Building

# A STUDY OF THE THERAPEUTIC VALUE OF A DIURETIC (THEOBROMIN SODIUM SALICYLATE OR DIURETIN) IN ACUTE EXPERIMENTAL NEPHRITIS (STUDY XVI)

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This study was undertaken with the idea of ascertaining whether or not there was any experimental evidence in support of the claim made frequently by clinicians that diuretics are contra-indicated in many cases of acute nephritis because they act to increase the work of the kidney and are irritants which may augment the pathological process already existent in the kidney. Clinicians holding this view regard diuretic drugs as harmful in cases of acute nephritis. If diuretics are harmful in acute nephritis animals with experimental renal lesions similar to those in acute nephritis in man should be unfavorably influenced by diuretic drugs. This series of experiments was planned to determine whether or not this was the case with one diuretic (theobromin sodium salicylate or diuretin).

Experiments were conducted chiefly along a comparative therapeutic line. An acute nephritis was produced in rabbits, and then a diuretic drug<sup>1</sup> (diuretin) was given to a part of the animals. The effect was judged mainly by the effect of the diuretic drug on the time elapsing between the dose of the substance used as a renal irritant and the death of the animal. In all of the experiments uranium nitrate was utilized as a renal irritant, since it produces an experimental nephritis in many respects similar to that occurring in human beings. Rabbits were the animals selected because a considerable number of experiments previously made for other purposes with these animals had given us a knowledge of the effects that might be expected from the use of such renal irritants.

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<sup>\*</sup> There have been published previously a series of studies on experimental cardio-renal disease by Drs H A Christian, R M Smith and I C Walker. Studies I and II, Boston Med and Surg Jour 1908, clviii, 696, and 1908, clix, 8, Study III Jour Am Med Assn, 1909, lxi, 1792, and Studies IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV and XV, THE ARCHIVES INT MED, 1911, viii, 168-551.

<sup>1</sup> From the Laboratory of the Department of Theory and Practice of Physic Harvard University.

<sup>\*</sup> This work was done under a grant from the Proctor Fund for the Study of Chronic Diseases.

<sup>\*</sup> Manuscript submitted for publication in THE ARCHIVES March 31, 1913.

1 The drug used was purchased under the trade name of diuretin from two retail drug stores. No difference in effect was observed between the two.

In Series 1 to 6 uranium nitrate was administered subcutaneously, and diuretin was used in watery solution administered with a stomach tube. In Series 7 to 11 uranium nitrate was given intravenously and intravenous administration of diuretin was employed. In all eighty-two rabbits divided into several series were used. Each series was divided into subject animals and controls. In some series the subject animals and controls were arranged in parallel groups of approximately equal body weights and were given equal doses of the drug. In most of the series the drugs used were given in doses varying in size according to the body weight of the animal.

In the first series, twelve rabbits varying from 1,350 to 2,100 grams divided into pairs of approximately equal weights were used. All were given subcutaneously at twenty-four-hour intervals three doses of 5 mg of uranium nitrate. After the first twenty-four hours one of each pair of the animals was given 0.1 gm of diuretin by stomach tube and this was repeated daily in most cases until the animal died. The animals which received uranium nitrate alone were regarded as controls for the subject animals that received uranium nitrate and diuretin. In this series the nephritis produced was a severe one and the dose of diuretin was large. As a result many of the animals died quickly, as shown by Table 1. The corresponding animal was killed at the time of death of the other animal in order to compare the anatomical changes in the two groups of animals. In this series no very striking difference exists as regards length of life between the animals with and without diuretin. Nine out of the twelve animals died four days or less after the first dose of uranium nitrate, and in two days or less after the last dose. It is true that the three animals killed to tally with their partners had received diuretin and this might suggest a favorable action for diuretin, but in the light of subsequent experiments this seems rather a matter of accident, the dosage of uranium nitrate being too great to allow of any sharp demarkation between treated and untreated animals.

In the second series (Table 2) nine rabbits were given a daily diet of 150 gm of carrots per kilo of body weight. Uranium nitrate was given subcutaneously to all of the rabbits in a dosage of  $3\frac{1}{3}$  mgm per kilo of body weight for two doses, twenty-four hours apart. To half of the rabbits was given daily 0.235 gm of diuretin per kilo of body weight by means of a stomach-tube. In this series the animals receiving no diuretic outlived those receiving a diuretic (diuretin), as shown by Table 2.

In the third series (Table 3) six rabbits were fed as in the second series and each received subcutaneously  $3\frac{1}{3}$  mgm of uranium nitrate. For these animals the daily dose of diuretin was reduced to 28.6 mgm per kilo, respectively. All animals not receiving a diuretic outlived those receiving a diuretic. The average length of life of the rabbits receiving

uranium nitrate alone was 8.5 days, and of those receiving uranium and diuretin 5.3 days

In the fourth series (Table 4) the rabbits were treated in the same way as in the third series. Of these, one rabbit receiving diuretin may be said to have survived, as it died on the twenty-second day from a complicating empyema. Omitting this animal, the other two with diuretin lived an average of eight and a half days, and two controls an average of nine days. Omitting this one surviving rabbit, this series shows a shortened duration of life for rabbits receiving the diuretic drug.

In the fifth series (Table 5) the rabbits were treated in the same way as in the fourth series. Three rabbits survived, two with diuretin treatment, and one with no treatment. Of the non-survivors, one with diuretin lived six days, and two controls lived an average of six and a half days.

In the sixth series, three doses of uranium nitrate ( $3\frac{1}{3}$  mgm per kilo of body weight) were given subcutaneously on successive days. Twenty-four hours after the last dose diuretin was given in doses half the size of those used in the preceding series, namely, 14.3 mgm per kilo, and this was repeated daily. In this series all but one of the rabbits receiving diuretin survived, while the controls lived an average of ten days.

In the seventh series (Table 7) two doses of  $3\frac{1}{2}$  mgm of uranium nitrate per kilo of body weight were given intravenously at twenty-four-hour intervals, and to half of these rabbits was given intravenously on the day of the last dose of uranium 7 mgm of diuretin in 2 c c of water per kilo of body weight, and on the next day 14 mgm of diuretin in 4 c c of water per kilo of body weight. All of the rabbits died on the same day, two days after the last dose of uranium nitrate. These results indicated too large a dosage of uranium and so this was reduced in subsequent experiments to two doses intravenously instead of three. In this and subsequent series the rabbits were fed carrots and hay freely and had constant access to water.

In the eighth series (Table 8) two doses of  $3\frac{1}{2}$  mgm of uranium nitrate per kilo of body weight were given intravenously at twenty-four-hour intervals, and on the following morning 14 mgm of diuretin in 4 c c of water per kilo of body weight were given intravenously, and this dosage was repeated morning and afternoon. Series 9 (Table 9), 10 (Table 10) and 11 (Table 11) were treated in the same way. In these four series four animals survived, four with diuretin and none without diuretin. Of those dying during the experiments sixteen received diuretin, and their average duration of life was 4.56 days, seventeen did not receive diuretin, and their average duration of life was 6.23 days.

In all of the rabbits which died, microscopic study showed in the kidney typical acute nephritis of the uranium nitrate type, with extensive



necrosis of the tubular epithelium. Control experiments were made to show that diuretin in various doses by stomach-tube and intravenously, such as were used in these experiments, was not toxic for normal rabbits and that water in intravenous doses of 1 c. c. per kilo of body-weight twice daily did not produce any appreciable disturbance in the rabbits, when each was given over periods longer than those used in the experiments described above.

#### SUMMARY

Diuretin was given to rabbits in which an acute nephritis had been produced with uranium nitrate. In forty-one rabbits the uranium nitrate was given subcutaneously and the diuretin by stomach-tube, in forty-one rabbits each drug was given intravenously. The amount of diuretin varied from large doses to 11 mgm. per kilo of body-weight. The latter is equivalent to 1 gm. dose for an average sized man. A few rabbits in the first series were killed as controls of rabbits dying, in all other series the rabbits were allowed to live as long as possible. Of the entire series, twelve survived, nine of which had had diuretin three had not. In this number of survivors may be rabbits which, on account of high resistance did not have a severe acute nephritis. Such resistant animals have been encountered in other sets of experiments. Of those dying under experiment, the average duration of life for those receiving uranium nitrate subcutaneously and diuretin by stomach tube was six days of the controls (uranium nitrate subcutaneously) 6.91 days, the average duration of life for those receiving uranium nitrate and diuretin intravenously was 4.56 days, of the controls (uranium nitrate intravenously) 6.23 days.

#### CONCLUSIONS

Diuretin given to rabbits with a severe, fatal experimental nephritis, shortens the duration of life of these animals. On the other hand, nine out of twelve rabbits which survived the experiment had received diuretin. This work supports the view that in a severe acute nephritis a diuretic drug, such as diuretin is contra-indicated inasmuch as in the experiments diuretin shortened the lives of the animals. On the other hand, of the survivors a large proportion (three-fourths) had received diuretin. This rather gives support to the view that in less severe cases diuretin may be beneficial and so justifies the cautious use of the drug in moderately severe cases of acute nephritis. In the survivors it is not certain that acute severe renal lesions were produced, consequently deductions from these relatively few survivors are of less value than from the larger number dying during the experiments. Of course, it is realized in making deductions such as the above that they may not be applicable directly to conditions in the human being, for due allowance must be made for the many differences between man and the lower animals. The experiments, however, certainly support the view that diuretin as a diuretic drug may be harmful in a case of acute nephritis.

## TABLES SHOWING EFFECT OF DIURETIN ON RABBITS WITH EXPERIMENTAL NEPHRITIS

TABLE I

No of Rabbit	Weight Gm	Days of Life After Dose of Urianium Nitrate	Treatment
354		4 (died)	None
353		4 (died)	Diuretin 0.4 gm, 3 doses
344	1,440	3 (died)	None
343	1,420	3 (killed)	Diuretin 0.4 gm, 2 doses
351	1,640	4 (died)	None
352	1,690	4 (killed)	Diuretin 0.4 gm, 3 doses
350	1,730	4 (died)	None
349	1,780	4 (killed)	Diuretin 0.4 gm, 3 doses
345	1,800	4 (died)	None
346	1,810	4 (died)	Diuretin 0.4 gm, 3 doses
347	1,930	4 (died)	None
348	2,100	4 (died)	Diuretin 0.4 gm, 3 doses

TABLE II

382	1,400	28+ (')	None
385	1,420	5 (died)	Diuretin 0.235 gm per kilo, 3 doses
380	1,820	7 (died)	None
383	1,800	6 (died)	Diuretin 0.235 gm per kilo, 4 doses
381	2,000	27+ (')	None
384	2,020	4 (died)	Diuretin 0.235 gm per kilo, 3 doses

' Used for another experiment

TABLE III

388	1,510	8 (died)	None
391	1,510	5 (died)	Diuretin 28.6 mgm per kilo, 4 doses
393	1,750	8 (died)	None
396	1,770	5 (died)	Diuretin 28.6 mgm per kilo, 3 doses
392	2,190	9 (died)	None
389	2,090	6 (died)	Diuretin 28.6 mgm per kilo, 4 doses

TABLE IV

429	2,120	9 (died)	Diuretin 28.6 mgm per kilo, 7 doses
427	1,950	9 (died)	None
425	2,410	22 (died)	Diuretin 28.6 mgm per kilo, 20 doses
424	2,260	9 (died)	None
387	2,590	8 (died)	Diuretin 28.6 mgm per kilo, 6 doses

TABLE V

443	1,350	Survived	None
455	1,350	7 (died)	Diuretin 28.6 mgm per kilo, 5 doses
452	1,470	10 (died)	None
456	1,580	Survived	Diuretin 28.6 mgm per kilo, 60 doses
454	2,030	5 (died)	None
457	1,980	Survived	Diuretin 28.6 mgm per kilo, 60 doses

TABLE VI

479	1,550	13 (died)	None
478	1,600	Survived	Diuretin 14.3 mgm per kilo, 19 doses
486	1,620	8 (died)	None
477	1,770	11 (died)	Diuretin 14.3 mgm per kilo, 9 doses
475	1,740	9 (died)	None
482	1,820	Survived	Diuretin 14.3 mgm per kilo, 19 doses

TABLE VII

504		4 (died)	None
505		4 (died)	None
506		4 (died)	Diuretin 7 mgm per kilo, 1 dose
			Diuretin 14 mgm per kilo, 1 dose
507		4 (died)	Diuretin 7 mgm per kilo, 1 dose
			Diuretin 14 mgm per kilo, 1 dose

## TABLES SHOWING EFFECT OF DIURETIC ON RABBITS WITH EXPERIMENTAL NEPHRITIS

TABLE VIII

No of Rabbit	Weight Gm	Days of Life After Dose of Uranium Nitrate	Treatment
537	2,310	3 (died)	Diuretin 14 mgm per kilo, 1 doses
538	1,950	8 (died)	None
539	1,160	3 (died)	Diuretin 14 mgm per kilo, 3 doses
540	1,760	5 (died)	None
541	1,000	3 (died)	Diuretin 14 mgm per kilo, 3 doses
542	1,750	8 (died)	None
543	1,600	Survived	Diuretin 14 mgm per kilo 8 doses

TABLE IX

560	1,050	1 (died)	None
557	1,120	3 (died)	Diuretin 14 mgm per kilo, 1 doses
551	1,150	1 (died)	None
554	1,200	4 (died)	None
558	1,200	3 (died)	Diuretin 14 mgm per kilo 3 doses
553	1,900	8 (died)	None
550	1,950	Survived	Diuretin 14 mgm per kilo, 16 doses
552	1,810	10 (died)	None
561	1,400	3 (died)	Diuretin 14 mgm per kilo, 5 doses
559	1,500	6 (died)	None
556	1,310	Survived	Diuretin 14 mgm per kilo, 16 doses
555	1,250	1 (died)	Diuretin 14 mgm per kilo 4 doses

TABLE X

564	1,860	5 (died)	Diuretin 14 mgm per kilo, 6 doses
565	1,910	6 (died)	None
566	1,670	3 (died)	Diuretin 14 mgm per kilo 2 doses
567	1,820	6 (died)	None
568	1,150	1 (died)	Diuretin 14 mgm per kilo, 4 doses
569	1,820	5 (died)	None
570	1,910	Survived	Diuretin 14 mgm per kilo, 8 doses
571	1,210	1 (died)	None
572	1,350	5 (died)	Diuretin 14 mgm per kilo, 6 doses

TABLE XI

576	1,350	6 (died)	None
579	1,560	8 (died)	Diuretin 14 mgm per kilo 10 doses
585	1,450	6 (died)	None
586	1,610	7 (died)	Diuretin 14 mgm per kilo, 9 doses
578	1,750	8 (died)	None
584	1,810	7 (died)	Diuretin 14 mgm per kilo 9 doses
577	1,850	5 (died)	Diuretin 14 mgm per kilo, 5 doses
580	1,950	8 (died)	None
583	2,060	7 (died)	Diuretin 14 mgm per kilo 9 doses

Peter Bent Brigham Hospital—Carney Hospital

# A CASE OF INFANTILISM ASSOCIATED WITH PITUITARY NEOPLASM

E J MULLALLY, M D

MONTREAL

Illness depending on pituitary disturbances is becoming more frequently recognized. The case of infantilism here reported is presented as an example of an interesting condition worthy of addition to the records of pituitary disorders.

## CASE REPORT

*History*—H. H., male, aged 26 years, occupation errand boy, weight 70 pounds, height 3 feet 8 inches, entered the Royal Victoria Hospital on account of headaches, vomiting and vertigo. He was a full term healthy child of 9 pounds at birth, and grew quite normally and naturally until the age of 10 years, he has not grown any since. As long as he can remember he has had attacks of vertigo, and at times double vision. About every month he was troubled with an attack of severe frontal headache, which sometimes darted through to the occiput, it was as a rule much worse during the day than at night. Vomiting was another distressing symptom which later began to trouble him. It usually accompanied the headache, was explosive in quality, occurred sometimes after meals, but often independent of them. These attacks of headache, vertigo and vomiting would last two or three days, and between them he was comparatively well, and able, when he grew a little older, to do work as an errand boy. Within the past year or so these attacks have become more frequent, and at times more prolonged. Stiffness of the muscles of his legs have been also observed by him during this time, and objects appeared to move up and down, and very often appeared double to him. His voice and mental development never got beyond that of a boy of 10 years, and his appearance shortly before his death was of a fleshy boy of that age, it could hardly be credited that he was 26 years old.

*Examination*—The general contour of his body was suggestively feminine, his head was large and his forehead slightly prominent. He was mentally bright for a boy, he was sexually as a boy of 10, he had no desire to associate with young men of his actual age, his amusements were boyish—tops, marbles and such toys. His skin was pale, on the face it had a distinct yellowish tinge, not by any means jaundiced, the subcutaneous fat was well marked. There were no lymph node enlargements. His thyroid was not palpable. There was slight fulness of the mammary glands, no distinct enlargement, but on palpation in that situation the tissues were distinctly firmer to the touch than the surrounding structures. There was no hair on his body. The hair of his head was dry, straight and coarse. His genital organs were those of a boy. His chest was slightly barrel shaped, well formed, symmetrical. His pulse averaged 68 to the minute, of regular rhythm but low tension. His blood-pressure was 90 to 100 mm. of mercury.

There were no pathological reflexes present, no strabismus, nor nystagmus, but double optic neuritis developed shortly before his death. He was under observation off and on for three months, but his headache, vertigo, etc. ceased after his first few days in the hospital. His last entrance to the hospital was five days before his death, his headaches were severe (uncontrollable by the usual remedies) and vomiting was frequent, muscular twitchings of the legs and arms

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were present and he was very dull mentally. His urine for the first time was found to contain abnormal constituents: specific gravity was 1.012, no albumin or sugar, but acetone in abundance and a trace of diacetic acid. His temperature had ranged from 97° in the morning to 99° in the evening throughout his stay in the ward, rose to 101° twenty hours before his death.

*Necropsy*.—Examination of the body was made four hours after his death. An undersized male, apparent age 12 years. Diffuse light-yellow pigment in skin of face. Scanty eyebrows. Teeth were excellent and well formed. Eyes were gray, pupils were equal and slightly dilated, eyelashes long and curved. Chest was prominent, and the skin was absolutely white. Breasts contained some fat. There was no hair on the body at all. Abdomen was prominent and fat. Genital organs were small. The testicles had descended.

The scalp was thin and stripped readily from the skull which was thin and transparent. The dura was not adherent. The blood vessels of the dura were congested. There was an excess of fluid between the dura and the brain. There was no thrombosis of the sinuses. The sella turcica was widened and the pituitary was greatly enlarged; it was tensely distended, particularly the portion nearer the brain. The infundibulum and stalk were likewise distended. The portion of the pituitary which fitted into the sella turcica was 2.3 cm. from before backwards and vertically it measured 2.5 cm. It was accidentally incised during removal and about 10 cc. of bright yellow fluid which was found to contain numerous cholesterol crystals escaped. The wall of the cyst was thin and adherent to its inner surface. In the region of the posterior lobe were three or four small soft rounded gelatinous looking masses. At the bottom of the cyst in the locality of the anterior lobe was a mass of soft, light yellow very friable material, the remains of a degenerated anterior lobe. The wall of the cyst in this locality was thicker and contained calcified material. The stalk of the pituitary was widely distended and was hollowed out continuous with the infundibulum, so that there was a free communication between the cystic pituitary and the third ventricle. On section of the brain it was found that the anterior portion of the left cerebral hemisphere was hollowed out in the white matter and contained a turbid yellowish cholesterol containing fluid. The margins of the cavity were ill defined. Projecting into it from behind was a jelly like mass of reddish color continuous with the choroid plexus forming a soft watery mass as large as the pituitary itself. The posterior horn of the left lateral ventricle was not dilated and its walls were normal. The posterior horn of the right lateral ventricle was dilated though its walls were normal in appearance. The right choroid plexus was small apparently normal. In the neighborhood of the velum interpositum the white matter showed numerous punctate hemorrhages; the same condition was seen in the velum itself and in the posterior portion of the corpus callosum.

Sections of rounded masses found in the cystic pituitary show new growth consisting of slender branching lines of cells separated by a highly myxoid stroma, very rich in well formed capillaries. The cells at the edge of the columns are columnar, those in the center polymorphous; they are more or less vacuolated. Some of the stroma cells are spindle shaped, some are drawn out into multiple processes. A few lymphocytes and allied cells are scattered here and there around the capillaries. The tumor at the anterior part of the choroid plexus shows the same characters, save that the processes of cells frequently include spaces filled with colloid material, in a few places resembling thyroid colloid. In a few instances there seems no doubt that this change is the result of liquefaction of the myxomatous tissue already mentioned.

Diagnosis of tumor: cystic endothelioma.

Section of the cyst wall shows a fibro-cystic change, with here and there small areas of necrosis, while others show evidences of having been infiltrated with blood.

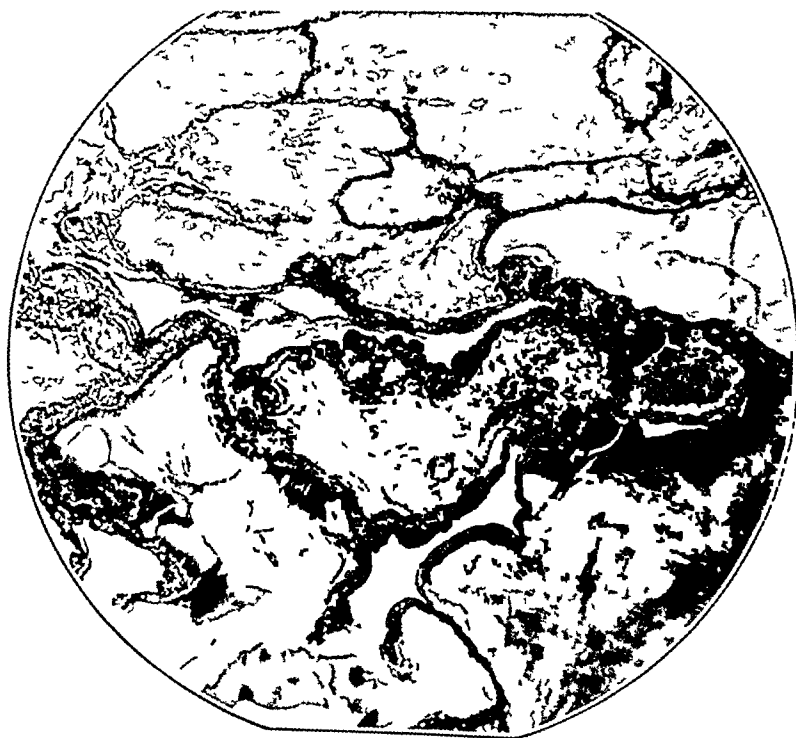
Sections taken from the floor of cystic pituitary in the region of the anterior lobe showed a large number of degenerated cells in which no nuclei are visible,

and whose cytoplasm usually stains very faintly with hardly an indication of the cell outline. A few cells are present which have a small dark-staining nucleus. A great deal of light yellow pigment is seen throughout the section. No blood-vessels are seen and no trabecular framework. The anterior lobe was therefore much degenerated.

The chest is well formed, the *Angulus ludovici* of the sternum is prominent. The costal cartilages are not calcified. The bone marrow of the sternum is pale and scanty. The subcutaneous fat was 2.2 cm in thickness and light yellow in color, the great omentum was full of fat. The diaphragm reached the level of the upper fourth rib on the right side, and the lower fourth rib on the left.

The thyroid was not enlarged, it is homogeneous. The right lobe measured 2.5 by 2.3 cm. The left 2.3 by 2 cm and the weight of the organ was 5.5 grams.

Sections show acini of varying size, rounded in shape and lined by a single layer of cells with deep staining nuclei, and distended with colloid material. The lining cells in some of the acini have a flattened appearance. There is no fibrosis, but excessive colloid.



Microphotograph of tumor in the choroid plexus, showing the lines of epithelioid cells enclosing spaces some filled with colloid matter, others with myxoid tissue. (Low power magnification.)

A large thymus particularly the left lobe was present, it was equal in size to what would be found in a child. Sections showed abundance of lymphoid tissue and Hassall's bodies were numerous. The proper cells were well defined and fat spaces were moderately abundant.

The liver weighed 650 grams and measured 19 by 12 by 5 cm. It was quadrilateral in shape rather flabby, the surface was smooth mottled with anemic areas. Differentiation was poor. The connective tissue was not increased, the cut surface was firm, the blood vessels were empty. Microscopic examination showed no noteworthy abnormality.

The pancreas measured 15 by 3 by 1.5 cm. It was soft and pink in color and normal on microscopic examination.

The spleen weighed 60 grams and measured 8 by 6 by 2.3 cm. The organ was firm, the surface was smooth and was purple red in color. Malpighian bodies

were hardly visible. The trabeculae were not conspicuous and the pulp was firm histologically.

Right kidney weighed 75 grams; it measured 8 by 5 by 1.9 cm. Juvenile in size. The width of cortex was 7 cm., medulla 1 cm. The capsule stripped easily; the surface was smooth and lobulated; the differentiation of cortex was good; the glomeruli were visible. The pelvis and the ureter were normal. Left kidney weighed 70 grams and had same characters as right. There was some cloudy swelling of the tubular epithelium.

The adrenals averaged 5 by 1.2 by 0.3 cm. The weight of both was 6 grams. They were atrophic in appearance; the cortex was pale in color; differentiation was good; the pigment was pale and sharply marked. The medulla was gray, and no necessary perivascular cortical tissue was present. Sections disclosed some vacuolation of the cells of the reticulate portion.

The testes were very small and waxy looking. Sections showed a preponderance of interstitial tissue, some of which was fibrous and some hyaline; the tubules were small in size, had little or no lumen, and were lined by a single layer of nucleated cells with a relatively small amount of cytoplasm. Many of the tubules here were replaced by fibrohyaline tissue. Very few interstitial cells are seen (cells of Leydig).

The other organs showed no abnormality.

#### SUMMARY OF FINDINGS

This case showed some remarkable features. Briefly, the clinical manifestations were: Marked underdevelopment of the skeleton and organs. "Infantile" development of the mental system. Brain tumor symptoms (headache, vomiting and optic neuritis). Feminine contour of body. Evenly distributed adiposity. Absence of body hair. Infantile genital organs. Low pulse-rate. Low blood-pressure. Subnormal temperature. Slight myxedema. Terminal changes in urine.

At necropsy: Cystic degeneration of the pituitary, with complete disappearance of the posterior lobe, and only a few degenerated cells representing the anterior lobe; free communication through the pituitary stalk with the third ventricle. Neoplasm of the choroid plexus extending into the pituitary. Internal hydrocephalus. Excessive colloid material in thyroid.

Vacuolation of the fasciculate layer of the adrenals.

Underdevelopment of the testes.

Small sized organs of the body generally.

Discoloration of the fatty tissue.

#### COMMENT

Infantilism has been written about chiefly by the French school of medical observers; they have a voluminous literature on the subject, and recognize distinct types. Conjectures have in many instances been made as to its causation, but few cases are recorded in which an autopsy examination disclosed the nature of the disturbance. Byron Bramwell, in his clinical studies, reports an interesting living case of infantilism, which agrees in most particulars (especially the age) with ours; it was supposed that the pituitary was at fault.

We have, however, a number of symptoms in our case which have been usually associated with the type of pituitary disturbance known as hypopituitarism. These symptoms are adiposity, absence of body hair, tendency to female bodily characteristics. Absence of sexual sense, subnormal temperature, low pulse-rate and low blood-pressure, although this latter symptom is supposed to be due to some disturbance of the adrenal, it may be that the adrenal is disturbed because the pituitary is disturbed. Also the slight myxedema changes may have resulted from a thyroid change, secondary to a primary pituitary disorder.

The outstanding feature clinically in this case was the infantile characteristics in a male, aged 26 years, and pathologically the marked pituitary changes. I have been unable to find in the literature another case in which a cystic pituitary communicated with the third ventricle through a hollowed out infundibulum and stalk. Such a condition is normal in a few of the lower vertebrates, but in man as well as the other members of the higher vertebrates it is not. The occurrence of a relatively benign neoplasm in the choroid plexus and of masses exhibiting the same characteristics on the walls of the cystic pituitary, as well as the clinical history, point toward a congenital origin for this abnormality. There may also exist a connection between the function of the pituitary and the choroid, as there may also be an embryological relationship between the choroid and the posterior lobe of the pituitary body.

Neoplasms in the pituitary have been often reported. The enlargements of the anterior lobe seen so frequently in cases of acromegaly have been often due to a new growth as well as to hypertrophy of the entire lobe. The type of neoplasm found in this case is rare. We have been unable to find any mention in the literature of finding this type of neoplasm in the choroid and pituitary in the same case. Ziegler mentions a condition occurring in the pituitary to which he gives the name "cystic endothelioma," the description of which agrees very closely with our case.

Farnell describes an interesting change in a pituitary tumor removed at autopsy from a female, aged 43, whose symptoms commenced when 36 years old, with headache, vomiting and optic neuritis, as well as cessation of menses. To quote some of his description of the findings:

Semicystic mass 3 cm in diameter continuous with the hypophysis and partially obliterating foramen of Munro. Both lateral ventricles dilated. Gritty granular material and numerous small cysts found in the tumor as well as colloid material. Microscopically it had an adenopapillomatous structure, and the older cells of the growth showed tendency to degeneration. Internal cells of papillae showed calcareous changes.

He conjectured that

Its median position and nodal relation to the neuroenteric canal, its continuity with the hypophysis, strongly suggest its histogenic relation not only to the buccal epithelium, but to the mandibular type composing the enamel-forming



organ of the tooth—hence its designation as a hypophyseal cholesteatoma—and also an adamantoma comparable to those tumors developing in the jaws from dental epithelium.

It may be seen from this interesting case that the pituitary is not immune to pathological conditions of an obscure nature. The suggestion as to the origin of the tumor in Farnell's case may be quite correct, and the name appropriate; yet it would be obviously impossible to collect within the confines of one small article all the obscure tumor formations of this organ. Suffice it, at any rate for the present, to say that our case presents another unusual type of tumor formation probably congenital in origin and that for some unexplainable reason it produced in the pituitary change which brought about in some obscure manner, physical and mental departures from the normal.

Many views have been presented about pituitary disturbances since Marie in 1885 made his interesting observation connecting pathologic changes in the pituitary with acromegaly—it was not, however, until a few years ago (1905), that Frolich recognized another type of pituitary disorder resulting in disturbances different from those occurring in acromegaly. Briefly stated the principal changes in this condition were in females adiposity and ceasing of menstruation—in males a tendency toward the acquisition of female bodily characteristics, with impotence.

Recent histological studies confirm what was previously held, that there are at least two distinct types of cells in the anterior or glandular lobe of the pituitary body. It is conjectured principally from their anatomical situation that these two types have distinct and separate functions, and probably discharge the products of their metabolism into the different channels, the one into the cerebrospinal fluid the other into the blood. The posterior lobe of the pituitary is composed of modified brain tissue, and in its action on blood-pressure it resembles the adrenal, although there are some important differences.

Even from this brief recital of the more outstanding anatomical features of the pituitary, it may be seen how rich the possibilities are for conjecture regarding its functions. It is not to be wondered at that this well-protected and isolated organ has only in recent years excited the curiosity of the research worker. While something has been accomplished, much remains to be done. It was only natural to expect that at the beginning of the work many unusual findings were recorded, there is much obscurity yet surrounding our knowledge of the functions of the pituitary. It is, however, fairly well established that the conditions of gigantism and acromegaly are due to changes of the anterior lobe of the pituitary. If the disturbance occurs before growth is completed gigantism appears, if after, acromegaly results.

It is also thought that the condition described first by Frölich (generally termed hypopituitarism) is caused by some unknown change, principally in the posterior lobe. The case already outlined would help to support such hypothesis. There was no posterior lobe discovered at autopsy, and the remains of the anterior lobe were in a state of degeneration. The central symptoms existing from his earliest remembrances, and subsiding after rest in bed for a few days, indicate a congenital origin for the brain findings. It is probable that the changes usually associated with thyroid and adrenal disturbances, and present to some extent in this case, may be attributed primarily to the pituitary.

As to the mental underdevelopment, it is difficult even to offer conjectures as to its causation. Only the fact was obvious that it was the mental development of a child and not that of a man of 26 years.

Thanks are due Dr. O. C. Gruner, director of the pathological department of the Royal Victoria Hospital, for permission to publish this case, as well as to Drs. C. F. Martin and John McChae for a synopsis of the clinical notes.

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## A CASE OF MYXEDEMA, WITH RECOVERY, AND SEVEN YEARS' AFTER-CARE NOTES\*

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Although the present-day knowledge of myxedema is well disseminated and the diagnosis usually easy, the comparative rarity of the disease contributes to delays and mistakes in recognizing the condition. The present case is a striking example of this, as the following letter from the patient herself will show:

"I must apologize for not writing for so long, but my time is taken up, it seems to me, and I hardly know how I spend my time. It has been a year now since I left the office and began doctoring and I do not see that I am one bit better. I have been to two specialists for my nose, throat and palate. They both said the palate and vocal cords were partially paralyzed. My tongue is also much swollen, which hinders my talking to some extent. They sent me to a specialist on the eyes, and he sent his report to Dr. ———. They had me examined by some kind of a specialist who examined, I believe, every nerve and organ in the body. He reported to Dr. ——— while I was there, and I heard a good deal. He thought it was Bright's disease. But Dr. ——— thought not as he had been keeping his examinations up so carefully. Then the other doctor said it was a tumor at the base of the brain, and wondered I had never had the headache or convulsions, or had never been unconscious. I am still a bad color, I still swell sometimes, my breath is dreadful. I have a rash over my body which looks like warts. I feel all right while in the house, but when I go out I feel very tired, especially walking up hill. I am still getting stouter."

The letter seemed characteristic enough to warrant a tentative diagnosis of myxedema and this was confirmed on her admission to Sheppard and Enoch Pratt Hospital, March 22, 1905.

*Family History*—The family history showed the following. The father died at 44 from pulmonary tuberculosis. He was said also to have had Bright's disease. One brother had had tuberculosis.

*Personal History*—Female, single, 41 years of age. Early history negative. She obtained a collegiate education and later took up stenography, acquiring considerable proficiency. Menstruation normal.

The onset of the disease dates back five years. A stiffness of the hands in using the typewriter was first noticed. Then hoarseness began and has continued throughout. A change in her appearance was soon noticed; her high color was replaced by a greenish, sallow complexion. Bodily weight steadily increased while her strength diminished. Two years ago she had several severe uterine hemorrhages and since then her general condition has been much worse. Menstrual periods occurred six to eight weeks apart. Sleep much disturbed by obstructed breathing and snoring. For the past year and a half has been constantly obstipated. Even in midsummer she made constant complaints of feeling

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† From the Clinic of the Sheppard and Enoch Pratt Hospital, Baltimore.

cold Conscious perspiration has been absent for the same period Mentally she has become dull and inactive, dislikes to make the slightest effort, and will not cross the floor for an article, no matter how much she desires it Depends on others entirely She falls asleep easily during the day even while occupied with some diversion

*Physical Examination*—Height, 155 cm, weight, dressed, 155 Hair coarse and dry Skin is pale, sallow, has a transparent quality, and is everywhere dry and scaly Subcutaneous thickening is wide-spread, most noticeable about



Fig 1—Myxedema, before thyroid administration, weight, 155

the clavicles, on abdomen and legs, the latter pit slightly on pressure Mucous membranes are pale and indicate considerable anemia Eyelids are somewhat edematous, giving a flat appearance to face Gums and uvula swollen Laryngoscopic examination negative Thyroid gland cannot be felt and is evidently diminished in size Heart shows reduplication of first sound Blood-pressure averaged 150 systolic, 115 diastolic

*Neurologic Examination*—Pupils react somewhat sluggishly to light Fundi show nothing but anemia Deep tendon reflexes equal and slightly exaggerated Pharyngeal diminished Cutaneous sensation, muscle sense and stereognosis

apparently unaffected. Coordination tests show some clumsiness. Muscle strength generally diminished. Dynamometer right 11, left 9. Gut negative except for weakness. Stands well in Romberg's position. Nictitation frequent. Voice has a husky and guttural quality.

*Mental Examination*—Consciousness and orientation intact. No evidence of hallucinations, sense perception, hallucinations or delusions. Judgment shows no gross disturbance and insight is sufficiently adequate so that she is cooperative. Subjectively patient's sensations present languor, inertia, weakness, somnolence, malaise and occasional headache. Objectively voluntary attention is lapsing and maintained with difficulty, psychomotor processes are slowed, and volition is

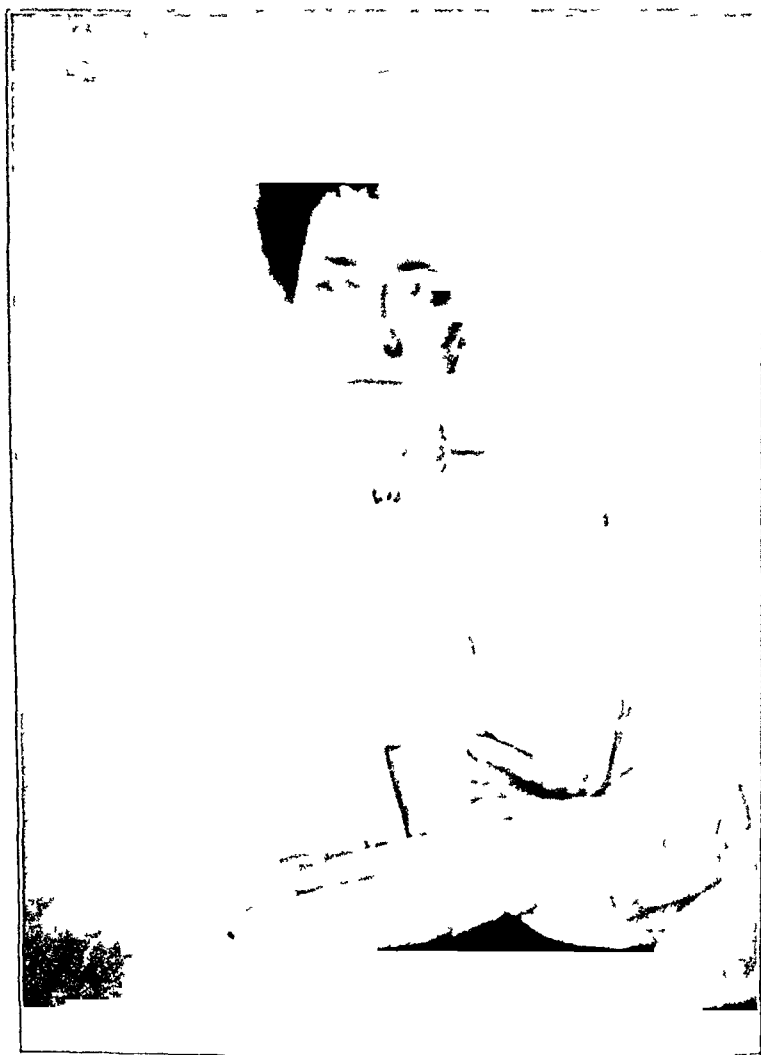


Fig. 2—Myxedema after two months' treatment. weight, 128

markedly impaired amounting to a high grade aboulia. Association tests showed increased reaction time. The affect presented apathy, sluggishness and indifference.

Urine examination on March 24 was as follows: 610 cc for twenty-four hours, strongly acid, faint trace of albumin, total urea, 9 grams.

Blood examination March 22: Red blood cells, 3,370,000, white blood cells, 7,200, hemoglobin, 45 per cent. Differential count of 695 cells: polymorphonuclears, 52.4 per cent, small mononuclears, 24.8 per cent, large mononuclears, 1.5 per cent, eosinophils, 19.7 per cent, basophils, 1 per cent.

*Treatment and Course*—On March 26 patient was put on 2 grains of desiccated thyroid gland three times a day. This was increased to 14 grains daily, and then dropped to 10, which was the dose she was taking on her discharge, May 20, 1905.

The following blood examinations show a progressive return toward normal

	March 27	April 10	April 30	May 19
R B C		3,170,000	4,136,000	4,800,000
W B C		6,200	6,000	5,500
Hemoglobin		55 %	55 %	75 %
Polynuclears	57.4 %	60.4 %	63.7 %	62 %
Small mononuclears	21 %	27.7 %	21.8 %	26 %
Large mononuclears	2.6 %	3.4 %	7.6 %	6 %
Eosinophils	16 %	6.8 %	6.1 %	5 %
Basophils	1.8 %	1.5 %	0.7 %	0.8 %
Normoblasts	5	6	2	0

Successive urine examinations gave the following results

	March 25	April 7	April 26	May 12	May 16	May 18
Twenty-four hour amount cc	690	570	660	510	960	1,000
Sp G	1.015	1.015	1.015	1.018	1.014	1.015
Urea, total, gm	6				17.2	17.8
Albumin	0	+	T <sub>1</sub>	T <sub>1</sub>	T <sub>1</sub>	T <sub>1</sub>

Body weight progressively declined as follows

April 1, 153, April 8, 147, April 15, 142, April 22, 137, April 29, 134, May 6, 132, May 13, 130, and May 20, 128, or about 2 pounds below her normal

The effect of the thyroid administration in the circulation was noted in a gradually developing tachycardia which reached a maximum of 120 about a week after inception of treatment, and then kept fairly constantly at 110 during the balance of hospital residence. Blood-pressure gradually declined from an average systolic of 150 to 115.

Temperature showed a slight irregular elevation, the highest point, 99.8, was reached about nine days after treatment was started.

After the second week of thyroid administration improvement was steady and fairly rapid. Sleep became undisturbed, the snoring and respiratory distress disappeared, physical strength gradually returned, although on discharge, she still complained of some difficulty in ascending steps. Appetite good. Bowels moved freely without cathartics for the first time in a year and a half. The anomalies in attention, volition and affect gradually were replaced by normal reactions, and on leaving the hospital May 20, the patient felt entirely well except for some physical weakness.

Four months after leaving the hospital the patient resumed her former position as stenographer and has kept steadily at work ever since. For several years she took the thyroid substance without interruption, but lately has skipped for two or three days and then resumed for a like period. In the seven years that have elapsed she has not missed a day at the office on account of illness, and feels as well as she ever did in her life. Her weight has not varied beyond the limits of 130-138.

## "GIANT-CELL PNEUMONIA"

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### REVIEW OF LITERATURE

An attempt has been made recently to isolate from the general group of lobular pneumonias a form in which the histological picture shows the presence of large multinucleated cells in the alveoli, not tuberculous in nature, a form of pneumonia which frequently follows acute infectious diseases of childhood, more particularly measles and pertussis<sup>1</sup>. This giant-cell formation occurs especially in association with desquamative bronchopneumonia a condition described by Buhl<sup>2</sup> as early as 1856. In 1872<sup>3</sup> he described in addition certain multinucleated cells occurring in the same condition, but his description is not so complete as to make certain that he saw identically the type of multinucleated cell under discussion. In 1876 however Friedlander<sup>4</sup> gave a more complete description of a multinucleated cell appearing in the pneumonic processes which he produced experimentally by cutting the recurrent laryngeal nerves and these cells certainly are identical with those described by Hecht. In 1889, Kromayer<sup>5</sup> made a complete study of the condition and considered it characteristic of the pneumonias of measles and pertussis. He described three types of giant-cell (a) a large multinucleated cell with large vesicular nuclei the cell being a fusion product of desquamated degenerate epithelium (b) a smaller syncytium with long spindle-shaped solid nuclei, probably originating from nuclear proliferation of the flat cells of the alveolus, (c) a multinucleated cell in masses of the cuboidal cells so frequently found in chronic and organizing pneumonias and considered by Friedlander to be attempts at regeneration. Aufrecht<sup>6</sup> described similar cells in 1894 and considered them to be fusion products

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<sup>1</sup> Submitted for publication in THE ARCHIVES March 5, 1913

<sup>\*</sup> From the Department of Pathology, Harvard Medical School

1 Hecht V Die Riesenzellen Pneumonie im Kindesalter Beitr z path Anat u z allg Path, 1910, LVIII, 263

2 Buhl, L Quoted by Buhl see footnote 3

3 Buhl, L Lungenentzündung, Tuberkulose und Schwindsucht München, 1872

4 Friedlander, C Experimental untersuchungen über chronische Pneumonie, und Lungenschwindsucht Virchows Arch f path Anat, 1876, LVIII, 325

5 Kromayer, E Ueber die sogenannte Katarrhalpneumonie nach Masern und Keuchbusten Virchows Arch f path Anat 1889 CXII, 452

6 Aufrecht, E Die Lungenentzündung Nothnagels Spec Path u Therap Wein, 1894, XIV, Part I, p 275

Durck<sup>7</sup> studied the condition very carefully and considered the giant-cell formation to occur particularly in diphtheria, insufflated exudate acting as foreign body. He considered the cells to be partly fusion products, partly the result of nuclear proliferation without cell division. Steinhaus<sup>8</sup> investigated nine cases of measles pneumonia, but found no giant-cells, he explained this by saying that the cases were of too short duration.

Galdi<sup>9</sup> made a detailed study of desquamative pneumonia, and although not referring to giant-cells directly, probably means to in speaking of colossally large desquamated cells. Hart<sup>10</sup> described them in his first paper and considers their formation a part of the proliferative process in long-standing pneumonias, but does not refer to them in a later paper. Friedrich Muller<sup>11</sup> refers to the giant-cells in Mehring's *Lehrbuch*, but apparently only echoes the studies of Durck. Hecht's<sup>1</sup> studies were most complete, not only including an anatomical study, but also making several experiments. Before that, however, other workers had produced the cells experimentally, notably Friedlander by section of the recurrent laryngeal nerves, Lahr<sup>12</sup> by intratracheal injection of staphylococci, Durck<sup>7</sup> by insufflation of pneumococci and of emery powder, Hecht, himself, by insufflation of sterile pus, of weak ammonia water, of weak solution of silver nitrate, of copper sulphate and of combinations of bacteria with insoluble irritants. Bacteria produced a pneumonia, but not giant-cells. Hecht states that he failed to produce a pneumonia by repeating Lahr's experiment, that is, by intratracheal insufflation of staphylococci. More recently giant-cells of the same character have been produced in anaphylactic pneumonia as described by Ishioka.<sup>13</sup> Reports of cases of long standing dust inhalation mention identical cells, and they occur also in cases of inhalation of irritant gases such as the fumes of nitric oxid. Wood<sup>14</sup> has reviewed the literature of these conditions very

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7 Durck, H. Studien über die Aetiologie und Histologie der Pneumonie im Kindesalter und der Pneumonie im Allgemeinen. *Deutsch Arch f klin Med*, 1896, *xlvi*, 368. Also, *Atlas und Grundriss der speciellen pathologischen Histologie*. München, 1900, *i*, 94.

8 Steinhaus, F. Histologische Untersuchungen über die Masernpneumonie. *Beitr z path Anat u z allg Path*, 1901, *xxix*, 524.

9 Galdi, F. Pneumonia desquamativa obliterans. *Deutsch Arch f klin Med*, 1903, *lxxv*, 239.

10 Hart, K. Anatomische Untersuchungen über die bei Masern vorkommenden Lungenerkrankungen. *Deutsch Arch f klin Med*, 1904, *lxxix*, 108. Also *Über die bronchitischen und postpneumonischen Obliterationsprocesse in den Lungen*. *Virchows Arch f path Anat*, 1908, *cxcvi*, 488.

11 Muller, F. Die Erkrankungen der Bronchien. Von Mehring's *Lehrbuch der Inneren Medizin*. Jena, 1905, p. 236.

12 Quoted by Hecht (see footnote 1).

13 Ishioka, S. Zur Histologie der anaphylaktischen Pneumonie. *Deutsch Arch f klin Med*, 1912, *cvi*, 504.

14 Wood, F. C. Poisoning by Nitric Oxid Fumes. *THE ARCHIVES INT MED*, 1912, *v*, 478.



completely and has added to it by his own anatomical and experimental studies

The origin and nature of the cells have been variously interpreted, but it is generally conceded that they must originate from the alveolar epithelium and that they are either products of fusion of more or less degenerate cells or are the result of nuclear proliferation without cell division. Nearly all the cases reported are of long duration and the vast majority have been in children and usually following some acute infection although a few, notably those of Aufrecht,<sup>6</sup> have occurred in patients of later life (40 and 72 years). This also is true of the cases



Fig 1—Low power (16 mm) showing inflamed bronchiole (A) and peribronchiolar granulation. The surrounding alveoli are filled with exudate and at B can be seen giant cells

due to dust or gas inhalation. The attendant inflammatory process is described sometimes as being moderately acute with infiltration of lymphocytes polymorphonuclears and fibrin formation, sometimes there is found only a moderate small round-cell infiltration into the alveoli and in still other cases the process is entirely a chronic and organizing one. Since the process of phagocytosis has been known the cells have been considered to have phagocytic powers by most of those who have considered this phenomenon in their discussion.

## CASE REPORT

*History*—V A, white, female, 18 months of age, was admitted to the Children's Hospital, Boston, Sept 18, 1911, service of Dr John L Moise, to whom we are much indebted for the clinical notes

The family history and previous history are not of especial interest except that the child was fed on equal parts of milk and water throughout its infancy, it gave a history of having been admitted to the Massachusetts General Hospital, Aug 19, 1911 with the diagnosis of pneumonia There is no history of any of the diseases of childhood It apparently recovered from the pneumonia and on Sept 13, 1911, was seized with an attack of vomiting followed by fever and cough A moderate diarrhea appeared, with yellow, watery stools containing a small amount of mucus

*Examination*—On admission, the child was found to be extremely rachitic and showed moderate enlargement of lymph-nodes, including tonsils Examination of the lungs showed dulness of entire left lung, with bronchial breathing irregularly distributed throughout and râles at the base, the right upper and

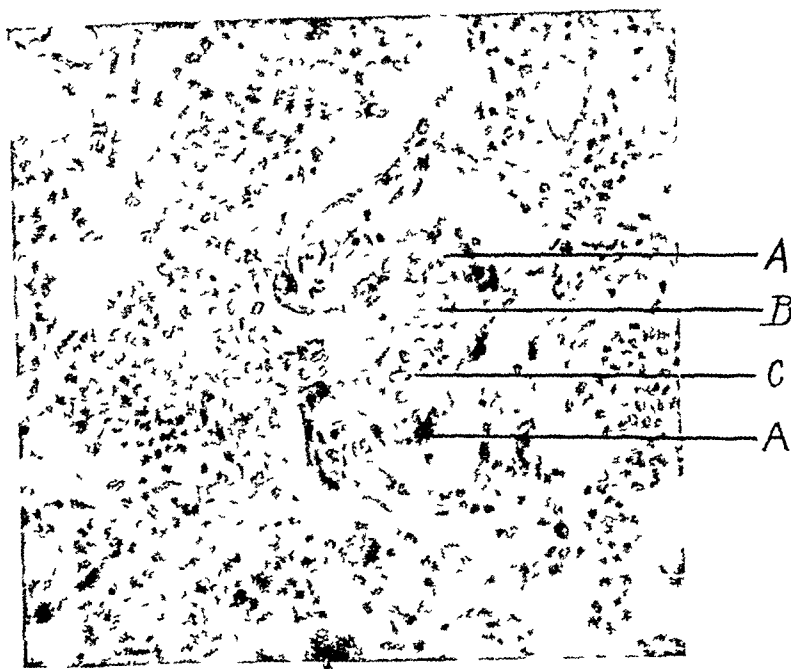


Fig 2—High power (4 mm) showing extensive synovial mass (A) lying in alveolus with bare walls At B is seen a mass of fibrin, at C are cells of exudate and nuclear fragments undergoing inclusion

middle lobes dull, with diffuse bronchial breathing, but no râles The chest and abdomen were otherwise normal Both ear drums showed scars of old perforations, but no discharge appeared

The temperature varied irregularly between 99 F and 104 F, respirations between 30 and 70 per minute, pulse between 120 and 160 per minute

Urine on admission was normal, but on September 30 showed trace of albumin and hyaline and finely granular casts

Von Pirquet tuberculin test was negative

Stools on October 1 were green and mixed with mucus, slight excess of neutral fat and great excess of fatty acids, no excess of soaps or starches

First leukocyte count September 19 showed 22 600 leukocytes of which 75 per cent were polymorphonuclears October 1 there were 14 000 leukocytes

*Necropsy*—Patient died October 2 and the autopsy (H11-964) was performed by Dr Albert F Boretta October 2, eighteen hours *post mortem* Exclusive of the lungs, the findings are as follows heart, normal, liver, cloudy swelling and

fatty metamorphosis, pancreas, normal, stomach and intestines, normal, spleen, acute hyperplastic splenitis, adrenals normal kidneys, well marked cloudy swelling, lymph-nodes of mesentery, acute hyperplastic lymphadenitis, thymus, moderate fibrosis

The lungs showed grossly considerable fibrinous exudation over the pleura. They were consolidated in irregular patches in left lower lower part of left upper lobes, right lower, right middle and lower parts of right upper lobes. The cut surface was moist and much bloody turbid exudate could be scraped off the surface. The reddish gray nodules of consolidation averaged 1.5 cm in diameter and the intervening lung substance was much congested, especially in the dependent portions. The remaining lung substance crepitated and was moderately congested. The bronchi and bronchioles showed no distention, but contained a large amount of viscid mucopurulent material.

*Microscopic Examination*—Sixty-three serial sections, 4 microns in thickness, and one slide from another block, sections stained with Mallory connective tissue stain, Verhoeff elastica stain, methylene blue and eosin, Ziehl-Nielsen carbolfuchsin stain, were studied.

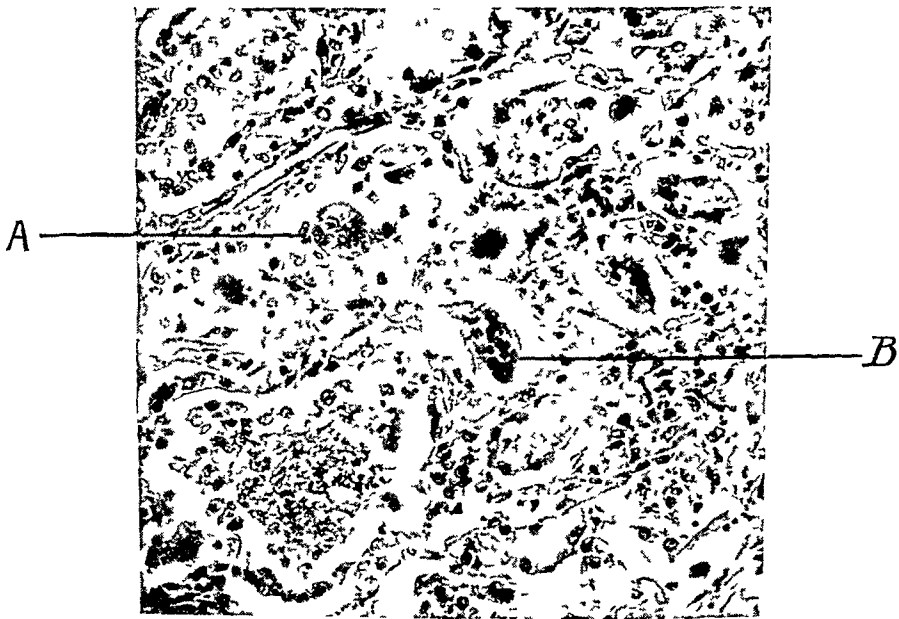


Fig 3—High power (4 mm) showing cell masses (A and B) one of which (A) resembles an ameba in form. In other serial sections these cells were found to be a part of one and the same extensive syncytial mass.

Histologically, the pleura was covered with a thin layer of fibrinous exudate under which was found a zone of granulation tissue and beneath that the denser connective tissue of the pleura proper. The exudate in the alveoli was found to occur in masses irregular in outline and usually surrounding a bronchiole. The intervening lung tissue showed only a slight amount of exudate and edema. The larger blood-vessels were distended and filled with blood and there was a very definite perivascular edema of the connective tissue. Finer examination showed that the bronchioles were filled with an exudate made up principally of more or less degenerate leukocytes together with desquamated degenerate epithelium, a few leukocytes, nuclear detritus and an occasional small mass of fibrin. The attached epithelium showed well marked cloudy swelling and in numerous places multinucleated cells, in one of which a mitotic figure was found. The cells correspond to the cell described by Friedlander.<sup>4</sup> About many of the bronchioles there was an areola of newly formed connective tissue extremely rich in capillaries and in association with this many of the bronchioles showed

partial or complete loss of their epithelium. No fragmentation of the elastica could be determined. The alveoli in the immediate neighborhood were filled with exudate similar to that in the bronchioles except that in a few alveoli an extremely rich fibrin content was found. The alveoli between the peribronchial pneumonic areas contained edematous precipitate, a few lymphocytes and much desquamated epithelium.

Scattered throughout the field, but seen particularly near the margin of the pneumonic masses, and also near the pleura, were large numbers of multinucleated cells. They occurred only in the alveolar spaces and not in the interstitial connective tissue. They measured from 60 to 80 microns in one diameter to 100 to 170 microns and more in the other diameter. They were irregularly outlined and presented all possible configurations from that of a crescent or even a complete circle to a distinct stellate shape. In places they looked like large amebas, in other places they resembled closely the Langhans type of giant cell. The protoplasm for the most part was coarsely granular and sometimes contained small empty vacuoles. The nuclei were sometimes large and vesicular with normally arranged chromatin, sometimes vesicular with peripheral clumping of the chromatin, sometimes they were spherical, sometimes elliptical, sometimes spindle shaped, the elliptical and spindle shaped nuclei usually were small and solid, the nuclei were arranged without any regularity whatever, sometimes centrally, sometimes peripherally, sometimes diffusely through the protoplasm. The protoplasm also contained lymphocytes, nuclear detritus, fragmented erythrocytes, polymorphonuclear leukocytes, and strands or masses of fibrin. Occasionally there was found a small unstained areola about a polymorphonuclear leukocyte, but never around any other cell or piece of detritus. Where these multinucleated cells appeared the alveoli showed no lining epithelium. For the most part the giant cells lay free in the alveoli, but frequently a small portion was found attached to the wall or even continuous with a layer of attached epithelium.

Special stains for tubercle bacillus and *Treponema pallidum* were negative. With methylene blue, cocci, sometimes in clumps, sometimes in chains, and small diplobacilli were found. Culturally, *Staphylococcus pyogenes aureus* was isolated.

In reconstructing the giant cells by the serial wax plate method, it was found that what appeared to be a number of giant cells in a given slide ultimately were connected and formed part of a large syncytial mass extending through a large number of alveoli and infundibuli. It could not be demonstrated that they were continuous with the bronchiolar epithelium, but they were definitely found to be a part of the alveolar epithelium, showing attachments to the alveolar wall in various places. When they lay free in the alveolar space there was no epithelium between them and the alveolar wall.

#### SUMMARY OF CASE

In reviewing the case it would appear that the child, without history of preceding acute infection, had suffered with pneumonia for seven weeks with a more or less complete remission in the midst of this period. Clinically, no unusual features were observed, nor was the gross morbid anatomy of the case out of the ordinary. Histologically, the two unusual features were the granulation tissue around the bronchioles and the giant-cell formation in the alveoli.

#### DISCUSSION

The peribronchiolar granulation suggests the possibility of an associated bronchiolitis obliterans. When Lange<sup>15</sup> described this condition

15 Lange, W. Ueber eine eigenthumliche Erkrankung der Kleinen Bronchien und Bronchiolen (Bronchitis and Bronchiolitis obliterans). *Deutsch Arch f klin Med*, 1901, Lxx, 342.

he noted the fact that marked alveolar desquamation accompanied it in many cases. Bronchiolitis obliterans in its earlier stages shows this appearance, but usually also shows fragmentation of the elastica which our case did not. Nor was there in our case any evident narrowing or dilatation of the bronchioles. No corresponding stage of organization was present in the pneumonic exudate. There is no doubt that this case shows an early stage of bronchiolitis obliterans<sup>16</sup>

The study of the giant-cells shows, first the fact that there is close anatomic connection between what a single section shows as a number of cells and the mass ramifying through numerous alveoli and infundibuli but not into bronchioles, second that there is obvious continuity of giant-cells with attached and desquamated alveolar epithelium, third that the fusion of the epithelia from the alveolar wall includes in the final product the cells, fibrin and detritus of the intra-alveolar exudate, a stage being shown in Figure 2, fourth, that the elastica is entirely outside the giant-cells and thus that these are completely intra-alveolar, fifth that the protoplasm is never well stained and obviously is degenerate throughout.

This leaves two points for discussion, the histogenesis of the cells and the question of their vitality. The question of the formation of the cells is as to whether they are 'conglutinative' or 'proliferative' (Durck). In the study of nearly seventy sections from our case, only one mitotic figure was found and no evidence whatever of direct nuclear division. Thus although it cannot be said with certainty that nuclear proliferation can not account for the large number of nuclei in the cell it is probable that the vast majority are present as the result of fusion of single cells. The problem of the living activity of the cell must resolve itself into that of the most notable activity that can be seen in post mortem specimens, phagocytosis. The bodies within the cells have been variously interpreted as simple inclusions and as objects engulfed by phagocytosis. In the reconstruction of the cells it was found that various stages in the formation of the giant cells indicated that the epithelium fused either before or after desquamation and formed, perhaps first crescent-shaped figures and, in certain lines of section, ring-like masses surrounding the alveolus and containing in the middle the remnants of

16 In this connection note also the following papers.

Ribbert H. Virchows Arch f path Anat 1899 cxlvi 164

Herbig M. Ebenda 1894, cxxxvi 311

Fraenkel, A. Deutsch. Arch f klin Med. 1902 lxxiii 484 Berl klin Wchnschr 1909 xlv 6

Jochmann G. and Moltrecht: Beitr. z path Anat u. z allg Path 1904 xxxvi 540

Wegelin C. Ebenda 1903 xliii 438

Edens: Deutsch. Arch. f klin Med. 1906 lxxxv. 598

Vogel K. Virchows Arch. f path Anat 1911 cclvi 157

Wood F. C. See footnote 13

the original alveolar exudate, the central space was gradually obliterated and the more or less degenerate exudate was within the protoplasm of the giant-cell. It was noticed, however, that around the bodies of some of the included cells a small areola, suggestive of a digestive vacuole was found, but further examination showed that this phenomenon occurred exclusively around polymorphonuclear leukocytes. If this were to be considered a function of the giant-cell, it would seem reasonable to expect to find the same appearance around lymphocytes and erythrocytes as well as around leukocytes. This not being the case, it seems more likely to suppose that it represents the activity of the proteolytic ferment of the leukocyte. We have found, then, no positive evidence of phagocytic activity of these cells and no positive evidence of the fact that they are living active cells. Kromayer and others have found occasional mitotic figures and evidences of direct cell division, but no one has brought forward indisputable evidence of phagocytic activity on the part of the syncytial masses.

#### CONCLUSIONS

1 The case studied is one of bronchopneumonia of the desquamative type and is associated with an early stage of bronchiolitis obliterans.

2 No good reason has been given for assigning to the so-called "giant cell pneumonia" the dignity of classification as a pathological or clinical entity.

3 The giant-cell formation may occur following a wide variety of causes and is not characteristic of the pneumonias following only measles and pertussis.

4 The giant-cells are almost entirely the product of fusion of alveolar epithelium and present a wide variety of morphological characters, depending on the line of section.

5 There is no positive evidence for believing that these cells functionate as phagocytes.

# THE DETERMINATION OF THE DIASTOLIC PRESSURE IN AORTIC REGURGITATION

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The determination of the diastolic arterial pressure is second in clinical importance only to that of the systolic pressure. The average of the two approximates the mean blood-pressure and then difference the pulse-pressure, both of them values of considerable significance. Under favorable conditions, some notion of the systolic output of the heart can be obtained by dividing the pulse-pressure by the mean pressure, while the product of pulse-pressure by pulse-rate often gives us an idea of the absolute work done by the heart. The reason why the determination of the diastolic pressure by the general practitioner has been comparatively neglected seems to be that the simpler methods, as ordinarily practiced, give uncertain results, while the more accurate ones require a rather bulky apparatus.

## THE VARIOUS METHODS

The methods for estimating the diastolic pressure may be grouped into four classes, the palpatory, the visual, the graphic and the auscultatory. All of them depend fundamentally on the same fact. When the pressure in the cuff is higher than the systolic pressure, no blood flows into the arm. As the pressure in the cuff is slowly diminished a point is reached, at which the blood is just able to flow through the constricted artery. This marks the systolic pressure. As the pressure in the cuff continues to fall, larger and larger pulses pass down the artery until a point is reached at which the pressure in the cuff is just able to compress the artery during diastole. When the pressure in the cuff falls still lower, the amplitude of the pulsations again diminishes, since the peripheral portion of the arterial tree in the arm is now not quite empty during diastole. This fall in the pulse amplitude marks the diastolic pressure. With the palpatory method, the observer places one or more fingers on the radial artery, while the pressure in the cuff is allowed to fall. The first pulse felt at the wrist marks the systolic pressure, while the point at which the radial pulse first shows maximal pulsations marks the diastolic pressure. Or, better, the pressure in the cuff is gradually increased and the point at which the pulsations are maximal and about which they grow smaller is taken as marking the diastolic pressure. This method,

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in experienced hands, gives fairly good results. It, however, requires considerable training and involves a good deal of the subjective element. The comparatively unskilled observer obtains entirely untrustworthy results.

The visual methods involve the detection of the point of maximal pulsation by the eye. The excursions of the top of the mercury in the manometer or the vibrations of the needle in the dial manometer may be observed as the pressure falls, or the amplitude of the vibrations of a drop of alcohol in a capillary tube or of a pith-ball in a larger tube may be watched. The observation of the vibration of the column of mercury rarely gives satisfactory results. If the manometer tube is narrow, the vibrations are too small to be utilized, if wider, the portability of the instrument suffers. In any case, the accurate gauging of the point of maximal oscillation is a matter of difficulty, except perhaps in pulses of unusually large amplitude, and is dependent to an undue degree on the personal equation. The same is true in varying degrees of the other varieties of this method. Pal's sphygmoscope apparently gives the best results, but the apparatus is not easily portable, and observations with it are very tedious. Ehret has stated that at the point of diastolic pressure, and at that point only, the cubital artery can be seen to pulsate violently, but we have not been able, even after many trials, to confirm this observation.

Of the graphic methods, the best is that of Erlanger. A tracing is taken, as the pressure falls, of the brachial pulse as registered by the cuff itself. The diastolic pressure is marked not by the point of greatest oscillation nor by the point at which the oscillations first become smaller, since a diminution of amplitude often occurs above the diastolic pressure. In these cases, as the pressure in the cuff continues to fall, a further, sharper diminution of amplitude may be observed, and this marks the diastolic pressure. Sometimes, however, the fall in amplitude of the oscillations is so gradual that it is nearly impossible to identify this point. Moreover, this method, too, requires special training on the part of the observer, since he must watch both tracing and manometer simultaneously and instantly identify the point at which the pulse tracing shows a sharp fall in amplitude. This difficulty may to a degree be obviated by using a marker in connection with the tracing, registering each 10 mm of fall and later noting the pressure with which the decrease in amplitude corresponds. In those cases in which the fall of amplitude is not sharp, the difficulties of utilizing the apparatus are considerable.

The auscultatory method, on the other hand, is nearly free from these disadvantages. It was first introduced by Korotkow in 1905 at a meeting of the Society of Military Surgeons in St. Petersburg. The pneumatic cuff is placed around the arm in the usual manner, the pressure is



raised above the systolic level, and, as the pressure slowly falls the observer auscultates the artery at the bend of the elbow with a small stethoscope. The bell of the stethoscope should rest over the artery with the least possible pressure and should be close to the lower border of the cuff. With the first pulse that passes under the cuff, a sharp systolic sound is heard. As the pressure continues to fall, this tapping sound is replaced by a murmur, the latter again merges into a sharp sound, which first becomes dull and then ceases altogether. For convenience of reference, these changes of tone have been designated as phases, the first phase beginning with the first appearance of a sound, the second with the murmur, the third with the reappearance of the sharp sound, the fourth with the dulling of the sound, and the fifth with the cessation of all arterial sound. All observers agree that the beginning of the first phase marks the systolic pressure, and we believe this is in most cases the

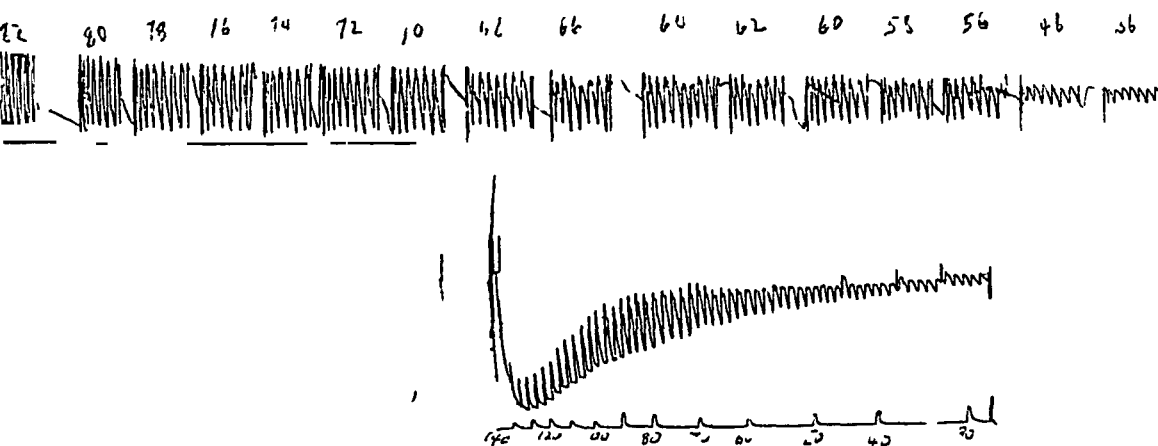


Fig 1—Aortic regurgitation with short fourth phase. On auscultation, with falling pressure in the cuff, the first phase begins at 132 mm Hg, the second at 122 mm, the third at 114 mm, the fourth at 68 mm, the fifth at 34 mm. The upper tracing was taken with the Eilanger apparatus, the pressure in the cuff being made to fall 2 mm between each set of pulse waves. The lower tracing was made with the same apparatus, the pressure in the cuff being allowed to fall continuously. The figures represent mm Hg of pressure in the cuff. It is obvious that the diastolic pressure, as recorded by the Eilanger apparatus, corresponds accurately with the beginning of the fourth phase.

most accurate way of determining this pressure. It is as much superior to the palpation of the radial as the sense of hearing is keener than the sense of touch. Students and all without a highly developed *tactus eruditus* nearly always obtain higher values with the auscultatory than with the palpatory method, and the more expertly the latter is done, the more nearly its results approach those of the auscultatory method. The exception to this rule is formed by individuals with small cubital arteries, in whom the Korotkow sounds are very feeble. In these cases the palpatory method is sometimes preferable.

## THE PHASE MARKING DIASTOLIC PRESSURE

The phase that marks the diastolic pressure has given rise to marked divergence of opinion, and it may be this uncertainty that is responsible for the comparative neglect of this method. Korotkow took the beginning of the fifth phase, at which all sounds disappear, to mark the diastolic pressure, and in this he has been followed by the great majority of writers. Among these may be mentioned, Kiylo, Janowski, Ettinger, Fellner, J. Fischer, Ehret, Schrumph and Zabel, Moritz, van Westenrijk, Gettings, and, according to Hirschfelder, Miss Allen and Mr. Engle, working in the Johns Hopkins Hospital. Hirschfelder himself, in his text-book follows Staehelin in taking the point at which the sound is loudest, as the diastolic pressure, an opinion which has not found many adherents. Lang and Manswetowa, in 1908, compared the auscultatory method with the apparatus of von Recklinghausen and found uniformly that the diastolic pressure was marked by the point at which the second clear sound took on a dull character. Hoover, Warfield and Dehio came to the same conclusion, the first by comparing the auscultatory method with the mercury manometer, the second with the sphygmograph and the third with the Erlanger apparatus. Warfield has confirmed his clinical observation by means of animal experiment.

## AUTHORS' TECHNIC

During the past six months, we have compared the Korotkow method with the results obtained by Erlanger's apparatus in a large number of cases and feel quite certain that it is the beginning of the fourth and not of the fifth phase that marks the diastolic pressure. At first we listened over the artery while making our Erlanger determinations. Later, fearing that the influence of suggestion might be leading us astray, we first made our auscultatory determinations, usually each of us independently, recorded them and then took our Erlanger tracings. In order to obtain the greatest possible accuracy in the latter, we took the brachial pulse tracings by means of the interrupted method, allowing the pressure in the cuff to fall 2 mm. Hg between each set of tracings and calling the first sudden fall in amplitude the diastolic pressure. In nearly all cases, the two methods coincided accurately. Where they differed, it was only by 2, rarely 4 mm., a difference well within the error of observation. Even these differences usually occurred only in those cases in which the interpretation of the Erlanger tracings was difficult.

The theoretic explanation of the fourth phase, as marking the diastolic pressure, is not far to seek. As the pressure in the cuff falls to the systolic pressure, the first pulses pass through. They find the artery below the cuff empty, and, distending it suddenly, produce a sharp sound. As the pressure in the cuff continues to fall, a point will be

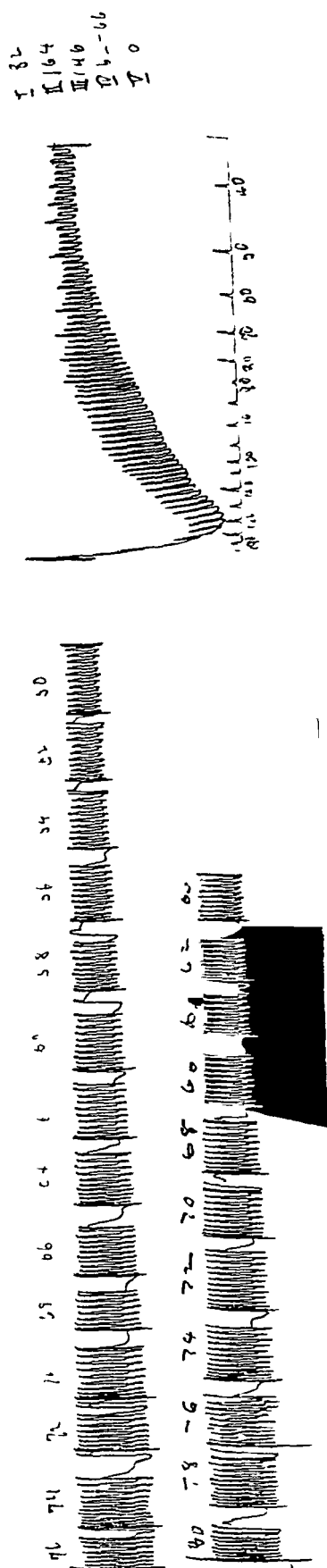


Fig 2 --Aortic regurgitation with long fourth phase On account of the patient's labored breathing, the upper limit of the fourth phase varies between 62 and 66 mm Hg. The tracings show the respiratory changes in amplitude, that sometimes render the interpretation of the Emlinger records difficult. Otherwise the same remarks apply as to Fig 1. The fifth phase is stated to begin at zero (Vo), merely as a convenient way of recording the fact that the dull sound can be heard over the cubital artery even after all pressure has been released from the cuff.

reached at which enough blood passes through to form whirls in the arterial stream, thus producing a murmur, which is usually loud enough to conceal the sharp sound. This phenomenon may be produced in any accessible artery by compressing it with the bell of the stethoscope. When the falling pressure reaches a point at which whirls are no longer produced in the blood-stream, the clear, tapping sound reappears. The artery beyond the cuff is still empty during diastole, and its sudden expansion by the spurt of blood that passes beneath the cuff at systole causes the clear, sharp note. As soon as the diastolic pressure is reached, however, a steady stream of blood begins to flow beneath the cuff, even between pulsations, and acting as a buffer, muffles the sound. The dull note, so produced, continues for a while until the sound is completely extinguished by the constantly increasing column of blood in the artery beyond the cuff. The correctness of this hypothesis is confirmed by the fact that if the observations are continued for an undue length of time, without releasing the pressure in the cuff, all of the sounds become muffled. What has happened is this. The blood that passes under the cuff, at first finds a resting place in the veins of the arm, beyond the cuff. After these have become fully distended, the blood must begin to accumulate in the arteries and a condition results similar to that occurring during the fourth phase.

#### ARTERIAL SOUND IN AORTIC REGURGITATION

Having thus confirmed the observations of Lang and Manswetowa and of Warfield, our attention was drawn to the conditions obtaining in aortic regurgitation. In this affection, the diastolic pressure is very low and the pulse-pressure abnormally high, producing a condition in the arteries similar to that obtaining in the brachial artery just beyond the cuff, when the pressure in the latter has fallen a little below the diastolic pressure. The result, in many cases, but not in all, is that a sound can be heard, on listening over any accessible artery, similar to that heard at the fourth phase, with Korotkow's method. That this is the dull note of the fourth phase and not the sharp note of the third can be shown by placing the bell of the stethoscope over the artery in the bend of the elbow while the pressure in the cuff is rapidly raised. At a certain point, which by the way marks the diastolic pressure, the dull note, heard from the very beginning, is suddenly replaced by a sharper and louder one. The great majority of the observers who have written on the auscultatory method, have taken pains to remark that the method is inapplicable to aortic regurgitation because of the persistence of the arterial sound. It was this statement that our investigation was intended to test. We have, so far, been able to compare the determination of the diastolic pressure by means of Erlanger's apparatus with the results obtained by the auscultatory method in eighteen cases of aortic regurgitation. In most

of them a large number of comparative determinations were made, often nearly daily for a considerable period of time. Our results uniformly showed that the diastolic pressure here as in other cases coincides exactly with the beginning of the fourth phase and that the method of Korotkow will uniformly measure the diastolic pressure in aortic regurgitation quite as sharply and accurately as in any other condition.

An interesting question involves the persistence of the fourth phase in this disease, that is, the presence of a pulse-sound in the artery even when there is no pressure in the cuff. A number of writers consider this phenomenon pathognomonic of aortic regurgitation. This is clearly an error. It was constantly present in only eight out of our eighteen cases and occasionally in two others. In the other cases, the duration of the fourth phase varied from 6 to 88 mm, the average being 32 mm. In these cases, the average pressure at which the fourth phase ceased was 33 mm. Moreover, we have seen three cases, one a bronchopneumonia and two exophthalmic goiters in which the pulse sound persisted down to zero pressure. In both, the pulse-pressure was high and the diastolic pressure low.

#### INFLUENCE OF RESPIRATION ON PRESSURES

Any attempt accurately to measure the blood-pressure must take into account the influence exerted on the latter by the respiratory movements. It has long been known that inspiration is accompanied by a fall in blood-pressure and expiration by a rise. The two do not coincide exactly, however, the pressure continuing to rise for a beat or two after the beginning of inspiration and to fall a beat or two after the beginning of expiration. The same phenomenon occurs in man and can be observed in any Erlanger tracing. As the pressure in the cuff approaches the diastolic, fluctuations in the amplitude of the recorded pulse-waves can be seen that are synchronous with respiration. With quiet breathing, the fluctuations in pressure are slight, rarely exceeding a few millimeters. In cases of dyspnea, however, and especially in Cheyne-Stokes respiration, they may be so great (12 mm or more) as entirely to vitiate the results obtained with the Erlanger apparatus. In addition to the fluctuation of amplitude due to the deep respiration, there is, in Cheyne-Stokes breathing, due to heart disease, a steady increase in the amplitude of the pulsations during the period of apnea. In such cases, then, the diastolic pressure obtained with the Erlanger apparatus will vary considerably according as this point is reached during inspiration or expiration or during the beginning or the end of apnea. The same will be true of the systolic pressure. The results obtained will be largely a matter of chance. With the auscultatory method, on the other hand, no such difficulties can arise. It is an easy matter to determine the maximum and minimum limits of pressure at which the first sound appears and the maximum

and minimum limits at which the second sound becomes dull. The limits between which the systolic and diastolic pressures vary can thus readily be made out.

Recently there has come under our observation a condition in which the auscultatory method was the only one giving even approximately accurate results. The case was one of Addison's disease in which the pulse-pressure was so small that the excursions with the Eilanger apparatus were scarcely large enough to be recorded. With the auscultatory method the sounds, though feeble, were distinct and the dulling of the sound clearly marked.

#### CONCLUSIONS

Our conclusions thus are

1 With the auscultatory method the beginning of the fourth phase, that is, the dulling of the arterial sound, marks the diastolic pressure.

2 Since this point can readily be made out in aortic regurgitation, the auscultatory method is as applicable to this condition as to any other.

3 The persistent arterial sound is not pathognomonic of aortic regurgitation, being often absent in this disease and occasionally present in other conditions.

4 In cases with very low pulse-pressure, in those with marked dyspnea and in Cheyne-Stokes breathing, the auscultatory method is especially valuable, being often distinctly superior to the graphic method.

TABLE SHOWING PRESSURES DURING PHASES I, IV AND V OF AUTHORS' CASES

Phase	I	IV	V	Phase	I	IV	V
J. H.	128	72	60	L. J.	132	65	54
W. H.	150	45	0	J. C.	154	60	0
B.	130	58	0	V.	190	82	0
K.	130	104	88	S. A.	170	90	84
H. R.	147	54	0	J. R.	112	48	42
L. D.	110	77	62	R. G.	144	70	55
R. N.	154	66	58	C. C.	182	62	0
H. S.	178	52	0	R. M.	190	137	?
W. B.	145	70	50	H. W.	150	75	0

The above table shows Phases I, IV and V of our eighteen cases. A number of observations were taken on most of the cases. An average reading is given. The daily variations in a given case were seldom great.

In conclusion, we desire to express our thanks to Prof. George Dock, in whose wards at the Washington University Hospital most of the above work was done.

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# A CLINICAL INVESTIGATION OF THE CARBONIC ACID IN THE ALVEOLAR AIR

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The experiments of Mosso, Haldane and his collaborators, and of Yandell Henderson have shown that the maintenance of a definite percentage of carbon dioxide in the alveolar air of the lungs and in the blood is of prime importance to the organism and is maintained by a definite physiological regulation. They have also shown that over-ventilation of the lungs by hyperpnea, which reduces the concentration of the  $\text{CO}_2$  in the alveolar air below normal, gives rise to a feeling of weakness and giddiness exactly like that of mountain sickness, and when pushed to extremes, also to periodic breathing of the Cheyne-Stokes type.

Yandell Henderson has produced a good deal of evidence to indicate that the clinical manifestations of surgical shock may be brought about by a condition of acapnia, and Porges, Leimdoerfer and Marcovici have found acapnia present in cases of acidosis and in certain cases of cardiac dyspnea.

As the subject seemed to warrant further investigation from the clinical side, the following observations were made.

We take great pleasure in expressing our thanks to Drs Barker, Thayer, Halsted and Williams for the privilege of investigating cases in their respective services in the Johns Hopkins Hospital, as well as to the members of the house staff for their hearty cooperation.

In carrying on a series of investigations, along with other routine duties met with in the wards of a large general hospital, the first essential was the possession of a portable form of apparatus. The apparatus to be described below, which possessed all the essentials of a complete Haldane outfit, but which was not much larger than the case of a microscope and could be easily and rapidly transported to different parts of the hospital, was therefore constructed.

## EXPERIMENTAL APPARATUS AND TECHNIC

The apparatus consisted essentially of the Haldane long rubber tube and gas buret for collecting samples of air, connected with a Hempel absorption bulb containing a solution of one part by weight of potassium hydroxide in two parts of water.

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\* From the Physiologic Laboratory of the Medical Clinic, Johns Hopkins University, and the Medical Service of the Johns Hopkins Hospital.

\* Read at the meeting of the American Physiological Society, Cleveland, Ohio, Dec 31, 1912.

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The patient took between his lips a mouth piece made of a slightly flattened piece of glass tubing 1.5 cm in diameter, which was connected by a thin-walled tube of pure gum rubber with a brass tube 4 cm long from the side of which a T-tube 0.6 cm in diameter passed through a hole in the box lid to connect with the gas buret on the inside of the box. The further end of the wide brass tube was connected with a rubber tube of corresponding width 210 cm long which was coiled up like a trumpet and firmly wired in place on the outside of the lid. A curved Ochsner clamp inserted through a screw eye just above the soft rubber tube enables the operator to clamp off the latter quickly at the end of the subject's expiration, in order that the air in the long tube may be analyzed at leisure. The capacity of this tube was 370 cc and since the mean volume of residual air is about 150 cc it can be assumed that at the end of a forced expiration the proximal portion of this tube contained almost pure alveolar air.

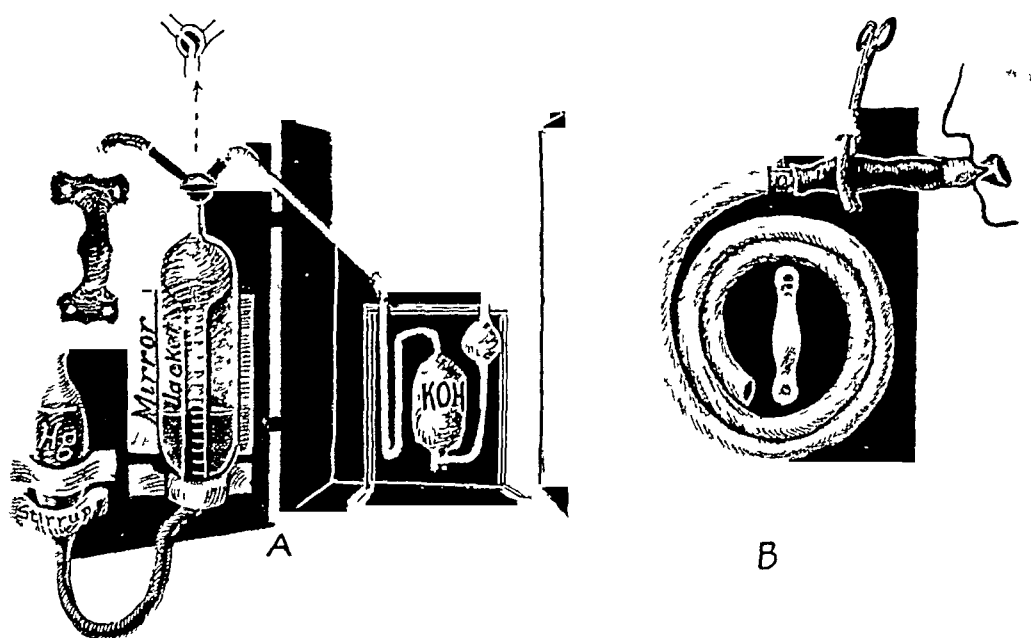


Fig 1—Portable apparatus for the determination of carbon dioxide in the alveolar air. A Inner aspect of the lid and box, showing the three way cock, the gas buret and water-jacket, the mercury vessel resting in the stirrup and the handle for lifting the lid. Within the box is shown the Hempel absorption bulb (KOH) and its connections. B External aspect of lid, showing the Ochsner clamp, the mouth-piece, the coiled rubber tube and the second handle for lifting the lid.

The gas buret in which the expired air was collected was specially constructed for the purpose and consisted of an unmarked bulb of about 75 cc (75.7 cc) capacity, above which there was fused a 3 way cock whose tubes connected on the one hand with the T-branch of the collecting tube and on the other by means of small bore (1 mm) barometer tubing with the Hempel absorption bulbs. On the lower end of the bulb tube there was fused a small tube of 10 to 15 cc capacity graduated in 0.1 cc<sup>1</sup>. The bulb and the buret are enclosed in a water jacket 6 cm in diameter to keep the air within at exactly room temperature. The lower end of the gas buret is connected by a heavy rubber tube with a glass vessel of about 100 cc capacity preferably the bulb of a

1 In the first experiments a bulb of 35.7 cc capacity was used without the water-jacket, and the connections between the parts were made with rubber tubing. The results obtained with this small instrument did not differ materially from those obtained with the larger water cooled bulb.

100 cc pipet which can be left to rest on a padded stirrup of metal placed on the door of the box a little below the level of the buret and a few inches to the left of the latter. The air is drawn into the buret by lowering this mercury vessel, or more conveniently by having it rest in the stirrup when the 3-way cock is opened. When the latter is closed the exact volume at atmospheric pressure is ascertained by raising or lowering this vessel until the top of the mercury menisci in both vessels are at exactly the same level. The leveling is somewhat facilitated by fixing a small mirror on the door behind the buret and raising and lowering the mercury vessel until the two menisci and their images are seen at the same level (Fig 1). In order that the air within the bulb should remain saturated with moisture, 0.5 cc of water slightly acidulated with dilute acetic acid is left floating above the mercury and the volume of the air is read from the lower edge of this water meniscus rather than from the upper edge of the mercury meniscus. A stock bottle of this acidulated water is kept on hand and is colored pink by the addition of dimethylaminoazobenzol in order to show always that no potassium hydroxide has been carried back into the bulb. After the volume of expired air has been measured, the CO<sub>2</sub> content may be determined by connecting the free arm of the 3-way tube with the Hempel absorption bulbs, preferably by means of an intermediary arm of fine bored glass tubing (barometer tubing) with short rubber connections. The 3-way cock is then turned to open into this arm and the air forced completely out of buret and bulb and into the Hempel bulb by raising the mercury vessel. When all of the air has been forced out of the bulb, the stop cock is again turned off full so that no air can return and the mercury vessel returned to the stirrup. The expired air is left in the absorbing bulb for one minute which is sufficient to absorb the CO<sub>2</sub> and then the stopcock is turned back and the air drawn back again into the bulb and buret until the KOH returns to its former level in the arm of the Hempel tube. The stop cock is once more turned off, the mercury leveled again, and the buret read. The difference between the two readings represents the CO<sub>2</sub> in the expired alveolar air. The percentage of CO<sub>2</sub> is calculated according to the equation

$$\text{Per cent CO}_2 = \frac{\text{First reading minus second reading}}{\text{Volume of bulb plus first reading}}$$

No correction need be made for temperature and pressure since they are the same for both readings, and therefore do not affect the percentage.

In collecting the expired air the subject is first made to breathe naturally, then to put the mouth-piece in his mouth and at the end of a quiet expiration expire as forcibly as possible, or give a violent cough, through the tube, and at the end of this forced expiration the tube is quickly clamped off. Several readings are taken, those which are most divergent are discarded and the average of the more or less coincident ones recorded. A few preliminary determinations must be made with each patient to accustom him to the use of the apparatus.

In investigating the more or less heterogeneous series of cases presenting themselves in the wards several points were kept uppermost in mind. First, to determine if possible whether the feeling of asthenia in convalescent patients and especially in patients who have gotten out of bed for the first time, is associated with the presence of acapnia. Second, whether the latter phenomenon is responsible for these symptoms in patients with enteroptosis. Third, the extent to which acapnia develops in cardiac dyspnea, and its relation to the mechanism of the latter.

It would have been particularly interesting for us to have determined the alveolar air in clinical cases of surgical shock, but those

TABLE 1—EXPERIMENTS WITH SMALL INSTRUMENT RESPIRATION NORMAL

No	Date	Name	Race	Sex	Age	Diagnosis	Symptoms and General Condition	Resp Rate	Form of Chest	Per CO <sub>2</sub> Cent
50	5/23/12	Tol	W	28	M	Inflam verumontanum and utricule	Walking around Looks healthy Much pain, however	16 to 20	Very well formed	49
56	5/25/12	Mey	W	30?	M	Paramyoclonus multiplex	In bed for a few days. Healthy except for jerking of muscles which makes patient very nervous	16 to 20	Fairly well formed	40
64	6/ 1/12	Dad	W	21?	M	Perfectly healthy	Leading natural life as orderly	16	Well formed	53
74	5/20/12	Hn	W	35?	M	In good health now Recently sick in bed	Not up to usual standard as yet	16	Rather deep chest Heavy built	51
75	7/21/12	E G	W	27	M	In fairly good health	Not robust Somewhat frail build	16	Well formed but small	40
76	5/28/12	E G	W	27	M	In fairly good health	Not robust Somewhat frail build	16	Well formed but small	41

Ammonium sulphate

Total ammonia

6.05

3.01

TABLE 2—EXPERIMENTS WITH LARGE INSTRUMENT RESPIRATION NORMAL

No	Date	Name	Race	Age	Sex	Diagnosis	Symptoms and General Condition	Resp Rate	Form of Chest	Per CO <sub>2</sub> Cent
1	7/17/12	Mary Bartens	W	30	F	Typhoid	In bed 1 month Not up yet Convalescent	20 to 24	Long and narrow	54
2	7/17/12	A R	W	11	F	Typhoid	In bed 14 days At height of fever extremely sick	20	Slender child Medium sized chest	52
3	8/10/12	A R	W	11	F	Typhoid	At home Has been walking about for 1½ weeks General condition good Improving rapidly	20	Slender child Medium sized chest	50
4	7/19/12	W R	C	25	M	Typhoid	In bed 35 days in hospital Still in bed Beginning convalescence Tired out from trials	24	Well built	49

5	7/10/12	C I	C	19	M	Typhoid	In bed in hospital 19 days virescence Has been up and about until a few hours ago No respiratory trouble of any sort	Beginning con-	24	Well built	43
6	7/17/12	C P	W	32	M	Mucous colitis (?)			20	Fairly well formed	58
12	7/20/12	Z T	C	24	M	Ulcer ventriculi			24	Well formed	43
26	7/24/12	K F	W	28	F	Congenital dislocation of hips Healthy otherwise			20	Fairly well formed	48
27	7/24/12	B P	W	64	F	Carcinoma of breast Otherwise well			20	Very slender small woman Small chest	40
28	8/ 5/12	B P	W	64	F	Carcinoma of breast Otherwise well			20		53
30	7/25/12	H B	W	19	M	Uncinariasis			20	Well formed	49
32	7/26/12	L J	W	40	M	C N S lesion			20	Well formed	44
34	7/26/12	A R	W	54	M	Gall-stones (operation)			20	Deep and barrel	49
37	7/27/12	T B	C	41	M	Direct inguinal hernia Perineal fistula Tuberc (?) Lues Ascites Pleurisy with effusion Rt. lung now collapsed Double hernia Otherwise well			20	Rather flat	47
38	7/27/12	H C	C	25	M				20	Right side depressed	46
41	8/10/12	A E H	W	42	M				20	Good average size	52
42	8/12/12	A E H	W	42	M				20	Good average size	44
44	8/21/12	J W	W	36	M	Adhesions of colon Chronic appendicitis			20	Good average size	50
45	8/23/12	J W	W	36	M	Adhesions of colon Chronic appendicitis			20	Good average size	52
46	8/12/12	J P	W	35	M	Gastric ulcer Pyloric stenosis Marked general enteroptosis			20	Phthisical Long, flat, narrow Lungs clear	55
47	8/14/12	J P	W	35	M	Gastric ulcer Pyloric stenosis Marked general enteroptosis			20	Phthisical Long, flat, narrow Lungs clear	52
48	8/11/12	J R	W	29	M	Appendicitis			20	Fairly well formed	55
49	8/12/12	J R	W	29	M	Appendicitis			20	Fairly well formed	50
50	8/24/12	H H	W	35?	M	Healthy			16	Large chest Rather deep Well formed but small	58
51	8/19/12	E G	W	27	M	Healthy			16		43

TABLE 3—EXPERIMENTS WITH SMALL INSTRUMENT IN CARDIOVASCULAR DISEASE

No	Date	Name	Race	Sex	Age	Diagnosis	Symptoms and General Condition	Resp Rate	Form of Chest	Pcp Co <sub>2</sub> Cent
51	5/22/12	Bod	W	53	M	Myocardial degeneration	No dyspnea In bed for 2 weeks Decompensation on admission	20 to 24	Barrel	43
52	7/22/12	Som	W	54	M	Myocardial degeneration Chronic nephritis	In bed many weeks Repeated decompensations Now compensated No dyspnea while perfectly quiet	24	Deep	39
54	5/21/12	Nlch	C	64	M	Myocardial insufficiency Aortic insufficiency	In bed 10 days Venesection 2 days before Very sick now Dyspnea	36 to 40	Barrel	33
57	5/20/12	Con	C	62?	M	Mitral stenosis + insufficiency Atherosclerosis	Gets out of bed during day Some dyspnea—more on exertion	30 to 36	Barrel	36
62	5/29/12	Wat	C	52?	M	Aortic insufficiency Slight myocardial insufficiency	Very slight if any dyspnea Some last night	36 to 20	Deep	36
63	6/1/12	Som *	W	54	M	Myocardial degeneration Chronic nephritis	Up during day for 1 week	20	Deep	45
65	6/2/12	C N	C	61	M	Myocardial degeneration Atherosclerosis Slight	In bed many weeks Entered with marked decompensation See No 13 under cardiacs with new machine Same patient	20	Barrel	33
66	6/3/12	Bod	W	73	M	Myocardial insufficiency Chronic nephritis	In bed for many weeks Entered with decompensation	24	Barrel	44
67	6/3/12	Sch	W	13?	M	Mitral stenosis + insufficiency	In bed for weeks Compensated Poor cardiac action	36	Fairly	40
72	6/11/12	Jef	C	22	M	Mitral + aortic insufficiency	In bed 7 days No dyspnea	16 to 20	Fairly	52
58	5/26/12	Med	C	58?	M	Myocard insuff Chr nephritis Atherosclerosis	In bed 5 weeks Very slight decompensation	36 to 40	Deep	26

\*See No 52 above Same case

TABLE 4 — EXPERIMENTS WITH LARGE INSTRUMENT IN CARDIOVASCULAR DISEASE

No	Date	Name	Race	Sex	Age	Diagnosis	Symptoms and General Condition	Resp Rate	Form of Chest	Per Cent CO <sub>2</sub>
7	7/17/12	C Z	W	45	M	Aortic insufficiency Aortic insufficiency Aortic insufficiency	In bed in hospital 3 weeks Up yesterday and to day for 2 hours Now in bed Nocturnal dyspnea previously Practically none now Pretty well compensated Five weeks in bed Good compensation now Formerly nocturnal dyspnea and myocardial insufficiency In bed now Has not been up Walking around for 1 week Up now No nocturnal dyspnea or cardiac asthma for some time Pulse 50 (digitalis) In bed 9 days Complaints of strange feeling over heart and stomach Gets up each day for several hours Has been in hospital for 5 months Came in in great decompensation Never fully compensated since Has been up in chair for 11 days Walks some No dyspnea In bed for 3 days Up for past 9 days in chair Very little walking No dyspnea Somewhat feeble	22	Somewhat barrel-formed	39
8	7/17/12	C H	W	51	M	Aortic insufficiency Aortic insufficiency Aortic insufficiency	Five weeks in bed Good compensation now Formerly nocturnal dyspnea and myocardial insufficiency In bed now Has not been up Walking around for 1 week Up now No nocturnal dyspnea or cardiac asthma for some time Pulse 50 (digitalis) In bed 9 days Complaints of strange feeling over heart and stomach Gets up each day for several hours Has been in hospital for 5 months Came in in great decompensation Never fully compensated since Has been up in chair for 11 days Walks some No dyspnea In bed for 3 days Up for past 9 days in chair Very little walking No dyspnea Somewhat feeble	22	Rather deep	63
9	7/18/12	P J	W	22	M	Aortic insufficiency Aortic insufficiency Aortic insufficiency	Walking around for 1 week Up now No nocturnal dyspnea or cardiac asthma for some time Pulse 50 (digitalis) In bed 9 days Complaints of strange feeling over heart and stomach Gets up each day for several hours Has been in hospital for 5 months Came in in great decompensation Never fully compensated since Has been up in chair for 11 days Walks some No dyspnea In bed for 3 days Up for past 9 days in chair Very little walking No dyspnea Somewhat feeble	20		53
10	7/18/12	Mrs O	W	54	F	Complete heart-block	Walking around for 1 week Up now No nocturnal dyspnea or cardiac asthma for some time Pulse 50 (digitalis) In bed 9 days Complaints of strange feeling over heart and stomach Gets up each day for several hours Has been in hospital for 5 months Came in in great decompensation Never fully compensated since Has been up in chair for 11 days Walks some No dyspnea In bed for 3 days Up for past 9 days in chair Very little walking No dyspnea Somewhat feeble	20 to 24	Small Somewhat flat	59
11	7/20/12	C N	C	64	M	Myocardial degeneration Arteriosclerosis Slight myocardial insuff now	Walking around for 1 week Up now No nocturnal dyspnea or cardiac asthma for some time Pulse 50 (digitalis) In bed 9 days Complaints of strange feeling over heart and stomach Gets up each day for several hours Has been in hospital for 5 months Came in in great decompensation Never fully compensated since Has been up in chair for 11 days Walks some No dyspnea In bed for 3 days Up for past 9 days in chair Very little walking No dyspnea Somewhat feeble	23	Barrel	53
15	7/21/12	J W	C	33	M	Aortic aneurysm	Walking around for 1 week Up now No nocturnal dyspnea or cardiac asthma for some time Pulse 50 (digitalis) In bed 9 days Complaints of strange feeling over heart and stomach Gets up each day for several hours Has been in hospital for 5 months Came in in great decompensation Never fully compensated since Has been up in chair for 11 days Walks some No dyspnea In bed for 3 days Up for past 9 days in chair Very little walking No dyspnea Somewhat feeble	20	Well formed	45
16	7/21/12	F R	C	49	M	Arteriosclerosis Emphysema Angina pectoris	Walking around for 1 week Up now No nocturnal dyspnea or cardiac asthma for some time Pulse 50 (digitalis) In bed 9 days Complaints of strange feeling over heart and stomach Gets up each day for several hours Has been in hospital for 5 months Came in in great decompensation Never fully compensated since Has been up in chair for 11 days Walks some No dyspnea In bed for 3 days Up for past 9 days in chair Very little walking No dyspnea Somewhat feeble	20 to 22	Fairly well formed	45
17	7/21/12	W S	C	15	M	Mitral insufficiency Myocardial insufficiency	Walking around for 1 week Up now No nocturnal dyspnea or cardiac asthma for some time Pulse 50 (digitalis) In bed 9 days Complaints of strange feeling over heart and stomach Gets up each day for several hours Has been in hospital for 5 months Came in in great decompensation Never fully compensated since Has been up in chair for 11 days Walks some No dyspnea In bed for 3 days Up for past 9 days in chair Very little walking No dyspnea Somewhat feeble	30	Fairly well formed	42
29	7/25/12	W S	W	17	M	Mitral insuff — stenosis Marked hypertrophy Pericardial effusion?	Walking around for 1 week Up now No nocturnal dyspnea or cardiac asthma for some time Pulse 50 (digitalis) In bed 9 days Complaints of strange feeling over heart and stomach Gets up each day for several hours Has been in hospital for 5 months Came in in great decompensation Never fully compensated since Has been up in chair for 11 days Walks some No dyspnea In bed for 3 days Up for past 9 days in chair Very little walking No dyspnea Somewhat feeble	32 to 34	Fairly well formed A little flat	36
35	7/26/12	C	W	56	M	Aortic insufficiency Arteriosclerosis	Walking around for 1 week Up now No nocturnal dyspnea or cardiac asthma for some time Pulse 50 (digitalis) In bed 9 days Complaints of strange feeling over heart and stomach Gets up each day for several hours Has been in hospital for 5 months Came in in great decompensation Never fully compensated since Has been up in chair for 11 days Walks some No dyspnea In bed for 3 days Up for past 9 days in chair Very little walking No dyspnea Somewhat feeble	28 to 30	Deep	45
36	7/27/12	J S	C	60	M	Myocardial insuff Arteriosclerosis Emphysema	Walking around for 1 week Up now No nocturnal dyspnea or cardiac asthma for some time Pulse 50 (digitalis) In bed 9 days Complaints of strange feeling over heart and stomach Gets up each day for several hours Has been in hospital for 5 months Came in in great decompensation Never fully compensated since Has been up in chair for 11 days Walks some No dyspnea In bed for 3 days Up for past 9 days in chair Very little walking No dyspnea Somewhat feeble	20 to 24	Deep and barrel	54
43	8/24/12	I G	C	27	F	Aortic insufficiency Decompensated now	Walking around for 1 week Up now No nocturnal dyspnea or cardiac asthma for some time Pulse 50 (digitalis) In bed 9 days Complaints of strange feeling over heart and stomach Gets up each day for several hours Has been in hospital for 5 months Came in in great decompensation Never fully compensated since Has been up in chair for 11 days Walks some No dyspnea In bed for 3 days Up for past 9 days in chair Very little walking No dyspnea Somewhat feeble	32 to 36	Very fat deep chest	41
							On leaving hospital no dyspnea	36 to 40		39
								36 to 40		33
								40 to 24		358

TABLE 5—EXPERIMENTS WITH SMALL INSTRUMENT IN A NEURASTHENIC

No	Date	Name	Race	Age	Sex	Diagnosis	Symptoms and General Condition	Resp Rate	Form of Chest	Per Cent CO <sub>2</sub>
53	5/22/12	Stan	W	37?	M	Neurasthenia Constipation	Occupation (tailor), race, and home life account for condition No dyspnea	16 to 20	Fairly well formed	43

TABLE 6—EXPERIMENTS WITH LARGE INSTRUMENT IN NEURASTHENICS

No	Date	Name	Race	Age	Sex	Diagnosis	Symptoms and General Condition	Resp Rate	Form of Chest	Per Cent CO <sub>2</sub>
11	7/19/12	Mrs K	W	35	F	Neurasthenia	In bed 17 days Remarkable cure of neurasthenia Nothing but home life and race to account for state Complains of headache and weakness from blowing	22	Heavy set Fairly deep	50
6	7/17/12	C P †				Mucous colitis				
18	7/21/12	D S	W	38	F	Neurasthenia	First day in bed Race and home life explain condition	20	Well formed	49
31	7/28/12	A W	W	33	M	Gastric neurosis Looks neurotic	In bed 3 days Not very sick	20	Fairly well formed	34
33	7/26/12	T T	W	30	M	Psychoneurosis?	In bed 3 days No dyspnea Sick 11 years off and on	20	Fairly well formed	45
39	7/27/12	R F	W	42	F	Mucous colitis Secondary neurasthenia	No hyperthyroidism In bed 3 days No dyspnea Not ill, but looks worn	20	Fairly well formed	43
40	7/27/12	J D	W	46	F	Colitis Neurasthenia Slight enteroptosis	No dyspnea In bed now Up during day	20	Slightly flat	53

†See under Resp normals

TABLE 7—EXPERIMENTS WITH LARGE INSTRUMENT IN PREGNANCY

No	Date	Name	Race	Age	Sex	Diagnosis	Symptoms and General Condition	Resp Rate	Form of Chest	Per CO <sub>2</sub> Cent
19	7/22/12	D McK	W	25	F	Pregnancy at term	Second child Walking Shallow expirations Nervous No dyspnea, except on exertion	32	Somewhat flat	39
20	7/22/12	E D	W	28	F	Pregnancy at term	First child Walking Deep expirations Not nervous Dyspnea only on exertion	24 to 28	Well formed	42
21	7/22/12	M E B	W	23	F	Pregnancy at term	Fourth child Shallow expirations Not nervous Dyspnea only on exertion	20	Fairly well formed	53
22	7/22/12	E J	W	33	F	Pregnancy at term	Fifth child Exceedingly short expirations Haid for patient to follow instructions	24	Fairly well formed	43
23	7/24/12	K W	W	21	F	Pregnancy at term	Dyspnea on exertion First child No dyspnea except on rather severe exertion Excellent patient	24	Well formed	48
24	7/24/12	A R	C	26	F	Pregnancy at term	Second child Dyspnea on walking	32	Well formed	39
25	7/24/12	J M	C	24	F	Pregnancy at term	Third child Considerable dyspnea on exertion	24	Well formed	39

TABLE 8—EXPERIMENTS WITH SMALL INSTRUMENT IN TYPHOID FEVER

No	Date	Name	Race	Age	Sex	Diagnosis	Symptoms and General Condition	Resp Rate	Form of Chest	Per CO <sub>2</sub> Cent
60	5/26/12	Wol	W	20?	M	Typhoid	Twenty one days in bed Beginning convalescence	20 to 24	Fairly well formed	36
68	6/ 7/12	Bar	W	26	M	Typhoid	In bed 2 months Up for 3 days, 1 hour q d	20	Rather flat chest	54
69	6/ 7/12	Clem	W	28	M	Typhoid	Frail looking man	20	Fairly well formed	56
70	6/ 7/12	Wol	W	20?	M	Typhoid	In bed 1½ months Up 3 days 1 hour q d	20	Fairly well formed	40
71	6/ 9/12	Stee	W	16?	M	Typhoid? Clinical but blood culture neg	See Case 80 above (same case) First day up, ½ hour in chair Now in bed again In bed for 8 days No dyspnea Quite sick	16	Well formed	36



TABLE 9—EXPERIMENTS WITH SMALL INSTRUMENT IN MISCELLANEOUS CASES

No	Date	Name	Race	Age	Sex	Diagnosis	Symptoms and General Condition	Resp Rate	Form of Chest	Per Cent CO <sub>2</sub>
59	6/26/12	Will	C	32?	F	Diabetes (Formerly in tense acidosis)	In bed for many weeks. Carbohydrate free diet and NaHCO <sub>3</sub> Now up in day for 2 weeks. Shallow respiration	20 to 24	Fairly well formed	37
73	6/14/12	Ok	W	56	M	Bronchial asthma marked	In bed for several weeks most of day. Some dyspnea now—attack fairly started	24	Barrel	45
61	5/29/12	Bell	C	29?	M	Bronchial asthma	Constantly marked expiration Dyspnea	20	Deep barrel	64

TABLE 10—EXPERIMENTS WITH LARGE INSTRUMENT IN MISCELLANEOUS CASES

No	Date	Name	Race	Age	Sex	Diagnosis	Symptoms and General Condition	Resp Rate	Form of Chest	Per Cent CO <sub>2</sub>
14	7/20/12	T R	C	35	M	Septicemia? Nature of infection never definite	Gets up for 1 part of each day. Some little dyspnea when up. Now in bed. Appears sick	28	Fairly well formed	54

patients in whom the degree of shock was sufficiently high to be regarded as crucial tests it did not seem safe to subject the patient to the ordeal of this examination

We therefore tried to determine whether there might be any relation between acapnia and the production of symptoms of asthenia such as are met with in convalescents from long illnesses, typhoid fever, surgical operations and also in persons with enteroptosis. The results of determinations on such patients as shown on the chart falls within normal limits (4.0 to 5.5 per cent) in most cases, though in a few convalescents from typhoid fever they were a little lower. These results coincide well with the figures obtained on normal individuals by Haldane and his collaborators, especially Mabel Fitzgerald.

We also tried to determine whether the weakness, dizziness and similar sensations experienced by convalescents on first getting out of bed were associated with acapnia. This was studied in four patients. In two of these — a man who had just gotten out of bed after an operation for appendicitis and a patient with gastric ulcer and extreme ptosis of the viscera — there was a slight fall of alveolar  $\text{CO}_2$  (from 0.3 to 0.5 per cent), a little more than the diurnal variation. In one convalescent from an appendix operation there was a rise of 0.2 per cent in spite of the fact that he complained of weakness and some giddiness and light-headedness. One of the four patients, a convalescent from a double herniotomy, who also had these symptoms, showed a marked fall in the  $\text{CO}_2$  from 5.3 per cent down to 4.4 per cent. There was, however, no marked change in rate of respiration.

These figures all represent percentages well above the level of acapnia, although in only one of the cases was the fall sufficiently great to account for the occurrence of any such symptoms.

We also investigated the alveolar  $\text{CO}_2$  of a number of heart cases. It was difficult to investigate these in the most severe grades of dyspnea, because the mere act of making a very large forced expiration threw them into violent coughing spells and made them feel so ill that it was not possible always to repeat the observations often enough to secure concordant results. A considerable number of these cases gave results below the lowest level for normals and this was especially marked in those who had rapid respiration rates at the time of making the determination.

After this work was in progress we found a short article in the literature by Poiges and Marcovici describing similar findings of low  $\text{CO}_2$  in certain but not in all cases of cardiac dyspnea. It would appear that we have in cardiac disease two distinct mechanisms for the production of dyspnea.

1 Stasis and congestion in the pulmonary area, associated with difficulty in aeration of the blood. This may act either by reflex stimulation of the vagus endings in the lung or by increasing the  $\text{CO}_2$  in the blood bathing the respiratory center which will give rise to hyperpnea until the  $\text{CO}_2$  falls to its normal level.

2 Slow arterial circulation through the medulla, as in arteriosclerosis, aortic insufficiency and general failure of the circulation, which gives rise to symptoms of lack of oxygen in the latter and the formation of acids there quite independent of the  $\text{CO}_2$ . This acid intoxication overstimulates the respiration and gives rise to over-ventilation of the lungs, acapnia, and probably sometimes Cheyne-Stokes breathing, for Pembrey and his collaborators have shown that the latter can be stopped by inhalations of  $\text{CO}_2$ . It is probable that such cases can be benefited by rebreathing, but we have not been able to answer this question as yet.

We had one patient with Adams-Stokes disease with complete heart-block, who was not having any attacks or dyspnea at the time of determinations, whose alveolar  $\text{CO}_2$  was normal.

A number of observations were made on pregnant women near term who had slight dyspnea, most of whom were a little below the lower limits of normal, which might be easily accounted for on purely mechanical grounds, though the possibility of a mild acidosis such as has been assumed by Poiges and his collaborators cannot be excluded.

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## BOOK REVIEW

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INNERE SEKRETION Ihre physiologischen Grundlagen und ihre Bedeutung für die Pathologie Von Prof Dr Artur Biedl, mit einem Vorwort von Hofrat Prof Dr R Paltauf Second Edition Part One Paper Price, 26 marks Pp 534, with 151 illustrations Berlin Urban & Schwarzenberg, 1913

The first edition of Biedl's splendid compilation of the literature and his own experience on the glands of internal secretion, appeared in 1910. The early appearance of the new edition demonstrates how much need there was for such a work, and how well supplied the need was. But this is more than a new edition—it is an entirely new work, for while the entire book in its first edition was but about 400 pages the first volume alone of the second edition contains 130 more. The author seems to have felt that in his first work the limited use of space prevented him from going into the detail which the unsettled state of many of his problems really demanded for their presentation. The need for explanation by means of illustrations has been filled by twenty colored plates and a great number of black-and-whites. In this volume which follows in arrangement the first half of the original edition are covered the thyroid, parathyroids, thymus and adrenal, and related subjects. There can be no question that the work, which from the start has been the best thing of the kind available, is greatly increased in value by its augmented inclusiveness, and is made much easier of understanding and of greater educational worth by the abundant illustrations. It will be used as the first source of information concerning the ductless glands since it is the one extensive and modern collection of the latest developments of this growing and interesting part of medical science. Furthermore, it is much more than a compilation for Biedl himself being an active investigator in this field has analyzed the work of others with the judgment and insight which only those who are themselves familiar with the methods and difficulties of research can possess. It is to be hoped that the second volume of this monograph will soon appear for since there is no bibliography in this it is to be assumed that that essential part of the work will be placed at the end.

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## THE HISTOPATHOLOGY OF THE NERVOUS SYSTEM IN PELLAGRA

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The study of the nervous system in pellagra has been made, to a very large extent, only with the older methods of staining, and it is our purpose here to present the findings in a series of cases in which the more modern methods have been used

The actual number of papers on the pathologic anatomy of the nervous system in pellagra is not very great and the conclusions reached are somewhat variable. By some the changes are regarded as characteristic and peculiar, whereas others see in the various findings only the expression of a generalized intoxication not in any way specific for this disease. The question is of some importance in relation to the widespread belief in the occurrence clinically, of a certain nervous and mental symptom-picture which is supposedly necessary for the diagnosis of pellagra. Another controversial feature, which stands out prominently, is the question concerning the relation of the vascular findings to the nervous changes and to pellagra itself.

The most recent<sup>1</sup> and extensive article on this topic is that of Kozowsky, whose results we shall have occasion to discuss in relation to our own findings. In this paper there is given a very extensive review of the literature beginning with the eighteenth century. As one might expect, Kozowsky comes to the conclusion that there is little of value prior to 1855, when there appeared a study of fourteen cases by Landouzy. Even at this time the brain was passed over as practically normal and attention was directed chiefly to the spinal cord in which were described softenings and sclerosis. As Kozowsky points out the

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\* From the Laboratory of the Illinois State Psychopathic Institute

\* Read in condensed form before the National Conference on Pellagra held at Columbia, S C, Oct 3 4, 1912

1 Since this was written there have appeared two excellent papers "Beitrag zur pathologischen Anatomie der Pellagrapsychosen" by A Rezza *Ztschr f d ges Neurol u Psych*, 1912, *xii*, 1, and "Des neurofibilles dans la pellagre" by Millant *Arch d Neurol*, 1912, *xxiv* No 2, p 312

material is open to question, and but little stress can be laid on these findings. In 1881 Paussier called attention to the occurrence of fatty degeneration in the vessels and nerve cells of the brain and the presence of numerous amyloid bodies. He speaks of rare and restricted arteriosclerosis and reaches the conclusion that pellagra is a toxic disease similar to other diseases brought about by intoxications with food poisons.

From this time on there is a gradually increasing definition of widespread changes in the nervous system. In 1883 Tonnini, besides meningeal changes, described fatty degeneration of anterior and posterior cornual cells. Hieronimus, in 1885, spoke of small-celled infiltration of the brain and ependyma with widening of the perivascular and pericellular spaces, proliferation of the ependyma of the central canal and inflammatory foci in the gray substance of the cord in corresponding regions. Neusser noted clouding and thickening of the brain membranes with adhesions and also atrophy, sclerosis or softening of the spinal cord. Marchi called attention to insufficient staining as evidence of degeneration of the fibers in the posterior columns, anterior horns and the spinal roots.

In 1889 appeared an important work on the spinal cord by Belmondo based on twenty cases. He divided the changes into acute and chronic. The former were found in those cases ending clinically with the so-called typhoid-pellagra, and consisted in changes which belong to the pathological picture of an acute meningomyelitis. The chronic changes consisted in sclerosis of various tracts of the cord, which in the severe cases were supposedly constant and represented a systemic combined posterolateral sclerosis. Accompanying this, there was pigmentary degeneration with atrophy and loss of processes in the ganglion cells of the sympathetic and spinal systems. He also mentioned the frequent occurrence of chronic leptomeningitis with "arachnitis ossificans."

Tuczek, 1893, described systemic sclerosis of the posterolateral columns of the cord and contrasted them with the lesions in tabes dorsalis. He also mentioned especially the pigmentary degeneration of the spinal and sympathetic ganglia and described the occurrence of proliferation of the glia without, necessarily, any implication of the vessels. This is also the first article in which granule cells (probably identical with those known under this name to-day) are specifically noted. He also pointedly minimizes the importance of the previous findings of cerebral vascular hyperemia, anemia, pial edema and meningitis, as well as occlusion of the central canal of the cord.

P. Marie, 1894, discussed and supported Tuczek's findings in regard to the posterolateral sclerosis of the cord and its distinction from tabes.

Lombroso, in 1898, published an important monograph giving the results of 113 autopsies. He laid much stress on the occurrence of men-

ingitis, which in some cases was purulent, arachnitis ossificans, pigmentation or fatty degeneration of the adventitia of the vessels, pigmentation of the ganglion cells of the sympathetic and whole central nervous system, degeneration of pyramidal and posterior columns, with numerous "granule cells" He also mentions softening of the cord with phenomena of poliomyelitis and numerous corpora amylacea in the spinal cord and sympathetic system

Babes and Sion, 1899, emphasized the pigmentation and chromatolysis of cells in the brain and the presence of pigment in pericellular and perivascular spaces, as well as a degeneration of fibers in the posterior roots, ascending cerebellar tract and Lissauer's zone Similar findings in many respects have been made by other more recent authors and will be discussed in dealing with the changes of particular elements of the nervous system All these papers deal, as will be seen, with the nervous lesions as a more or less primary condition There must now be mentioned papers by Kozowsky, 1904. Mannini, 1905 and Alpagon-Navallo, 1905, who laid particular emphasis on the presence of vascular lesions of arteriosclerotic character, which they claimed to be, to a large extent, the cause of the nervous lesions This same view was reiterated and amplified by Kozowsky in a more extensive paper in 1912 Lukács and Fabinyi, in 1908, as the result of the study of three cases, minimized the vascular findings in their relation to the nerve lesions

#### MATERIAL

The cases studied, fourteen in number, had all presented clinically, unquestionable evidences of pellagra. This was complicated in all but two by the presence of some form of mental disorder They may be subdivided into two groups, the first of which comprises those patients dying during the acute or subsiding stages of the pellagrous attack Of these there were eleven (We have also examined the nerve cell changes only, in one other case) Seven of them died at a short interval after the skin lesions had subsided, with clinical symptoms of "central neuritis" In the other five there were no symptoms, such as evidence of pyramidal tract lesion (Babinski reflex, jactatoid spasms, etc) to suggest central neuritis, although diarrhea with rapid and progressive emaciation and weakness were almost always present In only one of these twelve cases was there any complicating acute disease This patient suffered from an attack of facial erysipelas three weeks before death, which ran the usual course with recovery, but had as sequelae an abscess due to breaking down of cervical lymph-nodes and double otitis media Pus was still present in the neck at the time of death, but the abscess cavity was healing

The second group includes three patients dying of intercurrent disease (lobar pneumonia, acute pulmonary and pleural tuberculosis, and chronic pulmonary tuberculosis, respectively) at certain periods after the



subsidence of all pellagrous manifestations, that is to say, after apparent recovery. In one the interval was three and one-half months, and in each of the other two, eighteen months. Certain significant differences were observed in the histology of the cases in the two groups, which will be described in detail below.

The age of the patients at death ranged from 35 to 71 years. Five were suffering from senile dementia, ages 66 to 71 (two of these belonged to the interval cases). Four were old-standing cases of dementia praecox, aged 36, 50, 51 and 51, respectively. Two were suffering from a manic-depressive type of psychosis, aged 35 and 36. Two were not insane, aged 43 and 57. The clinical history of both of these last is published in detail in the Report of the Illinois Pellagra Commission.<sup>2</sup>

#### TECHNIC

1 Tissue fixed in 10 per cent formol and imbedded in paraffin (1) Toluidin blue (2) Thionin (3) Cresyl violet (4) Pappenheim-Unna (5) Heidenhain's iron-hematoxylin (6) Weigert's iron-hematoxylin and Van Gieson's stain (7) Weigert's resorcin-fuchsin stain (8) Osmic acid and toluidin blue for degeneration products

2 Tissue fixed in 10 per cent formol, after-mordanted in Weigert's glia fixing solution. Frozen sections (1) Alzheimer's method No IV for protoplasmic glia with Mallory's phosphomolybdic acid hematoxylin (2) Alzheimer's method No V with Mann's stain

3 Tissue fixed in 10 per cent formol, after-mordanted, embedded in celloidin and stained according to Mallory's glia fiber stain

4 Tissue fixed in 10 or 12 per cent formol. Frozen sections (1) Thionin, (2) Daddi-Herxheimer fat stain (3) Smith's nilblue sulphate for differentiating fats (4) Bielschowsky-Pollack silver impregnation

5 Tissue fixed in alcohol. Celloidin embedding. Thionin and toluidin blue

6 Tissue fixed in 10 per cent formol after-mordanted in Muller's fluid, embedded in celloidin (1) Weigert Kultschitsky Wolters myelin sheath stain (2) Marchi method

#### GROSS ANATOMY

The gross morbid anatomy of the nervous system was in no manner characteristic or pathognomonic. The skull presented no marked changes. At times there was thickening and at others thinning of the calvarium. The dura mater in the majority of cases was thickened, streaked with increased formation of connective tissue and in a few instances adherent to the pia mater. The pia-arachnoid was cloudy, opaque, edematous and thickened, at times lifted from the brain by the collection of fluid beneath it. The edema and thickening were most prominent over the convexity of the brain. In a few cases the pia-arachnoid was adherent to the underlying cortex. The spinal meninges showed similar changes to those noted in the cerebrum. Small bony plaques were occasionally observed. Neither *état criblé* nor punctate

<sup>2</sup> Cases J V and A D, Report of the Illinois Pellagra Commission (in press). Condensed Report, THE ARCHIVES INT MED, 1912, x, 123, 219

hemorrhages were met with in any case. The basal ganglia, cerebellum, pons and medulla were generally negative. In one case several hemorrhagic areas were observed in the mid-brain, but subsequent examination showed these to be, in all probability, artefacts.

#### MICROSCOPIC EXAMINATION

1 *The Pia Mater*—Great stress has been laid on edema and chronic inflammation of the pia by the older authors.

The pia showed constantly, changes of moderate severity consisting in thickening of the connective tissue with proliferation of fibroblasts. In a few cases the glia of the cortex was observed invading the thickened pia. This was especially true about the sulci. The more pronounced changes were in the vessels. The cells resulting from the proliferation of the vessel wall contributed largely to the formation of an exudate which was found in many cases. This exudate contained, besides the vessel cells, which were swollen and undergoing fatty degeneration, fatty and fibrinoid pigment granules and a few lymphocytes. Leukocytes were found in only one case, in which there had been an attack of erysipelas before death. Plasma cells were present in two cases, both complicated by pulmonary tuberculosis. No basophil cells were found in any case. The exudate was very small in amount in comparison with such diseases as cerebral syphilis, general paralysis, etc.

The thickening and vascular change was most marked over the convexity of the brain and was only severe in one case, in which it was universal, involving even the membranes lying within the folds of the cerebellum. Similar changes to those described above were also found in the pia of the spinal cord.

2 *Vessels*—The changes found in the vessels may be described under two headings according as they are acute or chronic. The former may be directly related to the pellagra, whereas the latter certainly are not.

The chronic changes were most evident in the larger arterioles and consisted in thickening of all coats with some proliferation of vessel cells. These latter were also swollen and often contained various pigment granules. Some of the endothelial cells were shrunken and pyknotic and frequently contained various granules of degenerative material. Twisting, curling and the formation of ropes by the twisting of three or four vessels, together with splitting of the intima and curling of the elastica, were met with only in those cases showing senility or chronic alcoholism. About the vessels numerous granules of fatty and fibrinoid character were seen and in a few cases granules showing basophilic properties. Granule cells (*Abraumzellen*) containing fatty and fibrinoid material were especially frequent.

The smallest vessels also to some extent showed the more chronic thickening, with, in a few cases, splitting of the intima. All the changes described above seemed to be related to age or general intoxication with alcohol. In no case was there observed any hyaline change in the vessel wall and in none were there any suggestions of occlusion. In three cases small hemorrhages were found, two in the spinal cord (gray matter) and in one in the mid-brain. These hemorrhages were not surrounded by any reaction zone or degeneration, the extravasated blood-cells and nerve cells lying within the hemorrhagic area stained well, the latter showing well-preserved Nissl granules. It was, therefore, concluded that they were probably artefacts and produced *post mortem*. No other punctate hemorrhages were observed in any case.

The more acute changes were observed in connection with the smallest vessels. The intima was thickened by proliferation and the endothelial cells were at times swollen and at others shrunken and pyknotic. Fatty degeneration was common and in a few instances the intima was found to be split, but few if any cells were present in the spaces thus formed. The muscle cells were proliferated, swollen and distorted, being elongated or sac-like, poor in chromatin and contained pigment of various kinds. The adventitia was thickened with proliferating cells showing various kinds of degeneration. These changes in some cases were extremely slight.

In one case in the whole of one set of specimens, there were found in the adventitial cells a number of metachromatic basophil bodies which presented various shapes, rosettes, curved and elongated masses with small projecting buds or lobules, etc. These bodies resemble very closely those described by Borrel in carcinoma, and to some extent those of Councilman in variola. They possibly represent, as suggested by Professor Zeit of the Northwestern University, a form of mucoid degeneration. They evidently require some special conditions for their staining, for we were unable to demonstrate them again even with an apparently identical technic and in the same brain. They stained a purplish red with thionin, somewhat similar to the color of the nuclei in these particular specimens and might, if not degenerative products, be cell nuclei. Some of the specimens do, indeed, somewhat resemble mitotic figures, and this explanation seems the more probable.

In all cases there was more or less perivascular infiltration, consisting of vessel cells, pigmented and degenerating lymphocytes, fatty and fibrinoid pigment granules, glia cells and *Abraumzellen*. No basophil cells were observed in any case. Plasma cells were found in considerable numbers in one case while in a second there were a few. Both of these patients had died of tuberculosis. Leukocytes were present in the exudate

in one case only, in which the patient had suffered an attack of erysipelas three weeks before death

New vessel formation and "process cells" were found rarely in one or two cases. *Stabchenzellen* occurred in numbers not exceeding the normal limits. Twisting of vessels and the formation of ropes similar to that described in the pia was present only in association with senility and chronic alcoholism. Widening of the perivascular spaces was also observed under the same conditions. The lumen of the minute vessels in the gray matter of the spinal cord was usually somewhat widened, and it was in this same position that the minute hemorrhages described above, probably artificially produced, had occurred.

No example of *état criblé* or blood-cyst was observed.

The exudate here described was of moderate degree in all cases and in some had to be sought with a high power in order to demonstrate its presence. It was not, in any degree, to be compared with the exudates which form such a striking picture, even with a low magnification, in specimens from general paralysis, lues cerebri, trypanosomiasis, etc. Although it probably has a relation to pellagra as an intoxication, it was also present in very similar degree and constitution in those patients dying at some considerable interval after the subsidence of all clinical evidence of pellagra, and in these can probably be related to the acute toxic and infective diseases which caused death. There is nothing in the picture to suggest a local invasion of the nerve tissue with micro-organisms.

As already indicated, much stress has been laid on the changes in the blood-vessels in pellagra by several authors, notably Kozowsky, Mannini and Alpago-Novallo. Kozowsky, especially, alleges that vascular lesions are the cause of many of the changes in the nerve tissue. This is particularly inexplicable for the reason that he selected his material with extreme care and laid down the following conditions before admitting it for use in studying the pathology of pellagra. He insisted on (1) the presence of characteristic symptoms in each of the skin, gastro-intestinal, nervous and psychic systems, (2) the absence of previous alcoholism, syphilis and bad surroundings, (3) the patients must be under 40 to 45 years of age. Yet in spite of these conditions, which he claims to have filled in all of his cases, he found frequently hyaline degeneration of the vessels at least in some organs of the body, with small focal softenings, old blood cysts, punctate hemorrhages and an *état criblé* in the brain. It might also be added that in most cases he found an advanced degree of sclerosis of the liver and spleen and describes the former organ as grating under the knife on section ("*Knirscht unter dem Messer, lässt sich nur schwer schneiden*") In view of our findings with cases considerably older and in some suffering from the effects of chronic alcoholism one

cannot but feel that there must have been some other factor at work. The importance of the vascular changes in relation to pellagra have also been minimized by Tuczek and more recently Lukács and Fabinyi.

3 *Neuroglia* — (a) *Fibers* In all cases there was more or less increase of glia fibers in the outermost layer of the brain cortex, which was especially marked in and about the sulci and around the vessels. In the network thus formed there were numerous amyloid bodies (Plate I, Fig. 26). In some cases the glia fibers were found invading the pia, causing adhesions between it and the brain. Similar increase of glia fibers was also present in the spinal cord, especially around the periphery and about the central canal. The increase of fibers was in no case as marked as is usually found in senile dementia.

(b) *Cells* — Although there were found several types of glia nuclei and cell bodies with thionin staining, no definite conclusions can be drawn from them, inasmuch as the normal limits of glia cells in this respect are poorly defined. In the superficial layers of the cortex were observed a large number of pyknotic distorted cells with long fibers the nuclei being star-shaped, lanceolate, biscuit-shaped, semilunar, etc. The protoplasm stained but poorly. Many pigment granules were present within these cells, staining bluish-red or pink with thionin. In the deeper layers of the cortex were found glia cells with a small, dark nucleus rich in chromatin and a small amount of faintly staining protoplasm. Also cells with a swollen, pale nucleus containing but a few fine chromatin granules and perhaps one or two pink nucleolus-like bodies. The nuclei frequently fill almost the entire cell body, and show many types of distortion into various bizarre shapes. A cell with a large nucleus of the same character and more deeply stained protoplasm was likewise seen. In the white matter there were two chief types of cell, one with a small dark and the other with a large pale nucleus.

Fatty degeneration of the bodies of the glia cells in the cortex was constant in marked degree. The bodies of these cells likewise contained other pigment material staining blue, green and reddish with thionin. In two cases, one of chronic alcoholism and the other with septic infection following erysipelas, a few giant glia cells containing two or more nuclei were found.

*Satellitosis* was constantly present in varying degree depending on the amount of chronic change in the ganglion cells. At times a number of satellites were found directly about a ganglion cell, sometimes forming a fence about it with a space between them and the ganglion cell. The satellite cells were especially numerous about the cells undergoing degeneration and the shadow cells. They were not present in increased number about the cells showing axonal reaction.

The *astrocytes* (Plate I, Figs 19-22) in all cases were definitely increased in number, especially in the deeper layers of the cortex and in the white matter, but not to the degree met with in general paralysis nor so marked as is usually found in senile dementia. The two most marked examples were cases of senility and chronic alcoholism.

These cells stained with Alzheimer's Methods IV and V, showed various interesting conditions. The cell processes were usually thickened and presented darkly-staining streaks of wavy outline. They frequently appeared to be broken. Occasionally the processes were small and thin.

The bodies of these cells were either large or comparatively small. Where large they were more homogeneous. Granular transformation of the protoplasm was frequently observed. The granules corresponded to the Alzheimer methyl blue granules, and probably indicate a degenerative condition. The nuclei showed various shapes and contained granules. They were crescentic, elongated, round or oval, central or displaced to the periphery of the cell. At times very little of the cell body was visible around a large, distorted nucleus from the vicinity of which issued darkly staining fibers. Occasionally a peculiar staining reaction was noticed in the cell bodies apart from the granularity.

The relation of the astrocytes to the vessels was variable. Some were found at a short distance from, but parallel to, the vessels, others encircled them, and still others existed apparently quite apart from the vessels in the surrounding tissues. Those in direct relation with the vessels were attached to the walls by insertion feet of various shapes and sizes. In many instances they were bent and twisted. In nine of the thirteen cases these insertion processes were definitely thickened (Plate I, Figs 19, 22), whereas in one they seemed definitely smaller than usual. This was an interval case, aged 71, the patient dying from acute pleural and pulmonary tuberculosis.

In seven cases a cystic degeneration (Plate I, Fig 19) of non-fatty character was found, similar to that described by Cerletti in cases of pernicious malaria, but also observed in other conditions. This cell picture should be differentiated from the cyst-like change associated with fatty degeneration. The cell protoplasm has disappeared in part or whole, to be replaced by numerous small or large, pale and apparently empty vesicles. These are present around the nucleus, and at times at some distance from it, or along some thickened process. From between the vesicles many processes, usually thin, can be seen to issue. The significance of this change is unknown, but its appearance suggests a degenerative condition. In all but one of the seven cases showing this type of cell, the patients had been either senile or the subject of chronic alcoholism. All three of the interval cases presented these cells and died with infective disease.

Giant astrocytes were found in five of the thirteen cases studied with the special glia stains. Two of them in younger individuals with manic depressive insanity and dementia praecox dying from pellagra, two with chronic alcoholism and one, an interval case, dying from chronic tuberculosis eighteen months after the disappearance of all symptoms of pellagra.

The increased number of astrocytes is not as marked as is usually found in senile dementia, but we cannot agree with Kozowski when he states that an increase of astrocytes is the exception rather than the rule.

The significance of an increase in astrocytes such as is here described is still undetermined. According to Alzheimer, Weber and Schroeder, it would indicate the presence of an active disease process, whereas Orlov and others find them more numerous in chronic conditions. The cases here studied can throw no light on this question, as both chronic and acute changes are present.

A variety of glia cell to which Alzheimer has particularly called attention and to which he ascribes much importance is the *ameboid transformation* of astrocytes and small glia cells. The ameboid glia cells (Plate I, Figs 23-24) have been found by Alzheimer particularly in recent and active diseases of the brain. Never in old hemorrhages, old-standing softenings, old cases of dementia praecox, in epilepsy after a long period free from convulsions nor in manic depressive insanity. On the other hand, they are present in severe infection deliria, alcoholic delirium, acute stages of dementia praecox, many cases of status epilepticus, many cases of general paralysis and lues cerebri, acute and subacute experimental intoxications, uremia, diabetic coma, sepsis, etc. Ameboid glia cells are seen most frequently in the deeper layers of the cortex and in the white matter. They present several forms (1) A small body with few pseudopodia and comparatively large nucleus, they are found chiefly about the vessels, (2) a cell with a large homogeneous body and numerous large pseudopodia. Frequently these cells are seen to surround a degenerating axone. Many surround a vessel matting together around it. Within their bodies are found pigment granules of various types. Granular change was frequent. Fatty degeneration was observed in one case which had suffered from erysipelas. Fat pigment was frequent. Ameboid cells were found in all cases in one or another form. It should be added that the interval cases all had some toxic or infective process to explain their presence.

Many astrocytes were seen undergoing the transformation into ameboid cells, sometimes while still clinging to a vessel by means of the insertion process (Plate I, Fig 21). Occasionally there were found ameboid cells, the bodies of which had coalesced and hence contained two or more nuclei. Along the vessels were found a number of examples

of this type of cell. Besides these, a number of small cells with round nuclei and a small amount of granular protoplasm were found lying along the vessels or scattered through the white matter. Processes were never seen issuing directly from these cells, but many thin processes radiated about them, and when examined in mass appeared to belong to the cells.

At this point attention may be directed to the condition of the *central canal of the cord* (Plate I, Fig 27), which was found to be occluded and changed in all but one of the cases. Such a condition is probably not abnormal in any adult (Schmaus, Ziehen, et al.), but it should be noted that here there seemed to be a definite central gliosis, and not merely a collection of debris and degenerated epithelial cells.

The processes of the ependymal cells interlaced with the fibers of the numerous glia cells to form a network in which were embedded amyloid bodies in varying number. The ependymal cells were rich in chromatin and when altered were usually swollen. Many layers of such cells were present, all semblance of the normal arrangement being lost. Small round nests of these cells were often observed scattered through the area occupied by the gliosis.

4 *Nerve Cells*—The *cyto-architecture of the cortex* was only slightly disturbed. The changes were most marked in the layers of large pyramidal cells. They consisted in paucity of cells with a change in their relative positions and increase of glia elements. In no case was there a disturbance as severe or marked as that seen in general paralysis.

The changes in the ganglion cells of the nervous system were extremely marked and of great importance. They may be divided for consideration into two groups (1) The indirect or axonal types of reaction, (2) the direct reaction types.

1 *Indirect or Axonal Reactions*—Two grades of intensity of this type may be recognized.

(a) *Typical Axonal Reaction* (Plate I, Figs 1-4, 9, 10, 18) —In this condition, which can be produced experimentally by injuries to the axone (Marinesco, van Gehuchten), the cell is swollen and rounded, the nucleus is displaced to the periphery where it may form an actual projection on the surface, or may even be extruded altogether. The tigroid substance has for the most part disappeared from the central portion of the cell, blocks, staining well, being often left around the periphery and especially in the base of the larger dendrites and a considerable mass around the nucleus. The nucleus is distorted, often oval or reniform, stains more or less uniformly with a pale color and there is a well-preserved nucleolus rich in chromatin.

(b) *Central Chromatolysis*—Cells presenting a body which is not swollen has a central well-preserved nucleus and darkly staining nucle-



olus The Nissl granules have largely disappeared from the central portion of the cell, but large blocks are present about the periphery and often also immediately about the nucleus. It differs from the last in the absence of swelling and displacement of the nucleus.

There was a marked difference between the cases examined at some interval after the pellagra attack and those in which death occurred during, or soon after, an acute outbreak. Of the *interval cases*, two died eighteen months, and one three and one-half months after the attack. The two former showed practically no axonal change at all, in the last it was present to a much less degree than in the acute cases. In one of the older cases no axonal change was found in the brain or cord even in the Betz cells or in the cells of Clarke's column, and only one anterior horn cell, situated in the dorsal region of the cord, presenting this change, was found. In the second many of the Betz cells were entirely healthy, although a few showed central chromatolysis without nuclear displacement. In the cord a few cells in Clarke's column showed typical axonal change as did also some of the cells of the semilunar ganglia of the sympathetic. In the case dying three and one-half months after the subsidence of the pellagrous attack a moderate number of the Betz and large pyramidal cells in the anterior central and paracentral convolutions showed axonal change, while most presented a picture of central chromatolysis without displacement of the nucleus. In this case also some cells showed a granulation with homogeneous, non-metachromatic, basophil particles not found in any other case. This change has been described in acute infective diseases and is possibly related to the tuberculosis, which was the cause of death.

In the *recent cases* axonal changes were severe in all, and in many involved practically all the Betz cells and many of the large pyramidal cells of the central convolutions. Similar changes were also found in the ganglion cells of the hippocampus, the dentate nucleus of the cerebellum, the central ganglia, and the nuclei of the cranial nerves.

In the cord these changes in the cells of Clarke's column were constant and often extreme, they were present in more or less of the anterior cornual cells in eight of twelve cases, in the posterior cornua in four (in one of these more marked than in the anterior cornua). Similar reactions were found also in the posterior root ganglia and in the cells of the semilunar ganglia of the sympathetic and of Auerbach's and Meissner's plexus in the intestine in the cases in which these were examined.

It is noteworthy that on the whole the Purkinje cells of the cerebellum were the best preserved cells of the whole brain. Some showed central chromatolysis, but none true axonal change.

The cell showing axonal reaction is, except in very severe degrees, capable of recovery and the above facts would suggest that the change is

the result of the condition, whatever it be, which underlies the acute pellagrous outbreak. During the interval the cells again resume, to a greater or less extent, their normal state. This type of reaction also seems to result from an injury to the neurone at a distance from the cell and such an hypothesis is well borne out by the absence of satellitosis about these cells noted above.

This one feature thus seems to bear the most definite relation to the acute pellagra attack. With it is probably to be related the scattered Marchi degeneration found throughout the nervous system. This particular picture of widespread axonal chromatolysis with special involvement of the Betz cells and those of Clarke's column has been noted by all workers on pellagra with modern methods of staining (Marinesco, Babes, Lugaro, Anderson and Spiller, Kozowski and others). As has already been noted by one of us, the picture is identical with that described by Meyer under the title of central neuritis. In a personal communication, this author assures us that none of his cases presented clinically a picture of pellagra. Attention may also be drawn, in this connection, to the publications on this syndrome and on the cytology of the brain in mental disorders by Cotton and Southard, Coriat, Somers, Orr and Coles. In a case of chronic alcoholism recently studied by us, there was, clinically and pathologically, a picture of central neuritis, and yet nothing to suggest a history of pellagra. Indeed, it would be impossible to distinguish microscopically between the specimens of this case and those here described. We must, therefore, conclude that pellagra is not capable of recognition *post mortem* (apart from the presence of the typical skin lesions). This is contrary to the opinion expressed by Kozowski in his very detailed report of cases with an excellent digest of the literature. It is of interest here to call attention to an oft-quoted case published by Righetti in which he specifically speaks of "polyneuritis" in a case of pellagra. This, as far as we have been able to find, is the only reference to the occurrence of neuritis in pellagra. The examination concerned only the spinal cord and peripheral nerves, and, while the axonal changes in the gray matter and sympathetic system were entirely similar to those described above, there was also a focal hematomyelia in the lumbar region with clinical symptoms suggestive of such a lesion. It is even more striking to find that, as specifically stated, there was no clinical history of pellagra, and the diagnosis was made chiefly on the grounds that the patient's mother had had pellagra, and she was living under conditions which favor its occurrence. Such a conclusion might be correct, but is not justified by the facts.

The interpretation of these changes is possible in only one way, namely, that such a picture as that presented in central neuritis is a mode of reaction to some harmful agent circulating in the blood, acting

on the axis-cylinder processes of the neurons at some point in their course. Further, it seems clear that this change may be brought about by various ultimate causes, although it is conceivable that the actual excitant of the reaction is the same in all and a product of body metabolism under morbid conditions.

2 *Direct Cell Reaction*—The result of immediate injury to the cell

Under this heading no distinctions can be drawn between the interval and recent cases. The various types of cell met with may be grouped under the following headings:

*Type 1*—Cell body shrunken and distorted with crenated edges but in some cases normal in size, more or less uniformly staining, pale in color. Nucleus rich in chromatin.

*Type 2*—Similar cell bodies with pale nucleus which may be of the same color or lighter than that of the cell body which may be reticulated. Within the nucleus or nucleolus are granules staining a bluish green with thionin. In some of these the nucleus is lost, with or without the nucleolus.

*Type 3*—Shrunken, uniformly dark staining cell body and dark nucleus sometimes filling almost the whole cell.

*Type 4*—Simple chromatolysis. Body normal or a little larger. Nissl granules are scattered diffusely throughout, rarefied and pale or present only as a fine dust. Nucleus approximately normal in staining and position. Nucleolus dark.

*Type 5*—Shadow cells, a more extreme degree of the same type as the last. Nucleus absent. The outline of the cell indistinct.

*Type 6*—Vacuolated cells. Nucleus present. No Nissl bodies. The cell body contains vacuoles.

All the above types of cell change, with the exception of Types 5 and 6, are found in all regions of the cortex in all cases, although generally most marked in the central and paracentral convolutions. Either shadow or vacuolated cells were present in all but four of fourteen cases. Similar changes belonging more especially to Type 3 were also found in the cells of the gray matter in the cord, most noticeably in the posterior cornua.

In association with these direct types of cell reaction there was more or less well-marked satellitosis. Such cell changes, first described by Nissl, have been the subject of numerous investigations (Marinesco, van Gehuchten). Marinesco, in particular, contrasts them with those we have described under the head of indirect or axonal reactions and considers that they are the result of direct injury to the cells themselves. Some of the types belong to the picture of acute change and have been produced experimentally by the administration of various intoxicants, such as lead, arsenic, etc., and are also observed in the acute infectious diseases, others are more chronic and represent the result of subacute or chronic poisoning. A further indication that these changes are the result of intoxication of the cells directly by noxious agents is also shown by the presence of satellitosis, which, as we have mentioned, is absent around the cell showing the indirect or axonal type of reaction. The other glial

reactions found in the cortex and white matter must also be regarded as indications of active acute and chronic disease processes, showing both progressive and regressive types of changes

The relation of these changes to pellagra is extremely difficult to determine. The fact that they are present in the interval cases cannot be considered as excluding a dependence on the pellagrous disorder, for similar changes can unquestionably be brought about by various toxic agents and must be regarded as merely a type of reaction to damage. All the interval cases were suffering from infections which might well cause a similar reaction to that of pellagra. Attention should also be called to the fact that two of our patients were suffering from pellagra without complicating psychosis or infectious disorder and hence one would be inclined to attribute the direct cell reactions and glial changes found in them to pellagra. In order definitely to settle the question of the presence of chronic cell change with satellitosis as a part of the pellagrous disease during the period when there are no clinical symptoms observable, it would be necessary to study uncomplicated (especially by chronic mental disorders) interval cases in which the patients died at a sufficient length of time after the acute attack to permit the disappearance of the nerve lesions which result from such acute exacerbation. This unfortunately, we have so far, been unable to do. The question is an important one, for if such changes do persist, there would be ample basis for the occurrence of a more chronic dementing pellagrous insanity, the existence of which must be still considered as *sub judice*.

*Fibril Changes* (Plate I, Figs 11-18) —The neurofibrils were successfully stained in ten of our cases and showed similar changes in all, including the interval cases. The changes found consisted in

- 1 Agglutination
- 2 Fragmentation
- 3 Loss of fibrils (in small cells only, with one exception referred to below)
4. A peculiar encircling of the nucleus and pigment masses with agglutinated fibrils, not, as far as we are aware, previously described in pellagra

In only one case (senile dementia of severe grade) were the fibrils found to be absent in large cells. In this case the fibrils, when present, showed the reticular formation usual in senile dementia. This case also showed advanced chronic Nissl changes in the cells, with reticulated protoplasm and extreme fatty pigmentation.

The reports of fibril changes in pellagra are somewhat scanty. Parhon and Papinian report one case in which they found complete loss of fibrils in the large pyramidal and Betz cells. This, as already pointed out, is certainly the exception. The neurofibrils have been the subject of exten-

## LEGENDS FOR PLATE

Figs 1-4 —Cells showing axonal type of reaction 1 and 2 from the cerebral cortex, 3, from the spinal anterior cornu, 4, from a sympathetic ganglion (Nissl staining)

Figs 5-6 —Pyramidal cells from the cerebral cortex showing fatty degeneration (Nissl staining)

Figs 7-8 —Pyramidal cells from the cerebral cortex showing basophilic degeneration (Thionin)

Fig 9 —Cortical pyramidal cell showing axonal change and fatty degeneration (Osmic acid and toluidin blue)

Fig 10 —Fatty degeneration and axonal change in a cortical pyramidal cell (Scharlach and hematoxylin)

Figs 11-18 —Fibrillary changes (Bielschowsky) In 14 note the double ring formation Figure 18 represents the neurofibril picture in a cell showing axonal change

Fig 19 —Astrocyte (Spider cell) undergoing cystic degeneration Note the thick insertion foot (Alzheimer IV)

Fig 20 —Astrocyte showing twisted insertion process (Alzheimer IV)

Fig 21 —Astrocyte undergoing ameboid transformation (Alzheimer IV)

Fig 22 —Astrocyte with thickened insertion process (Alzheimer IV)

Fig 23 —Ameboid glia cell (Alzheimer IV)

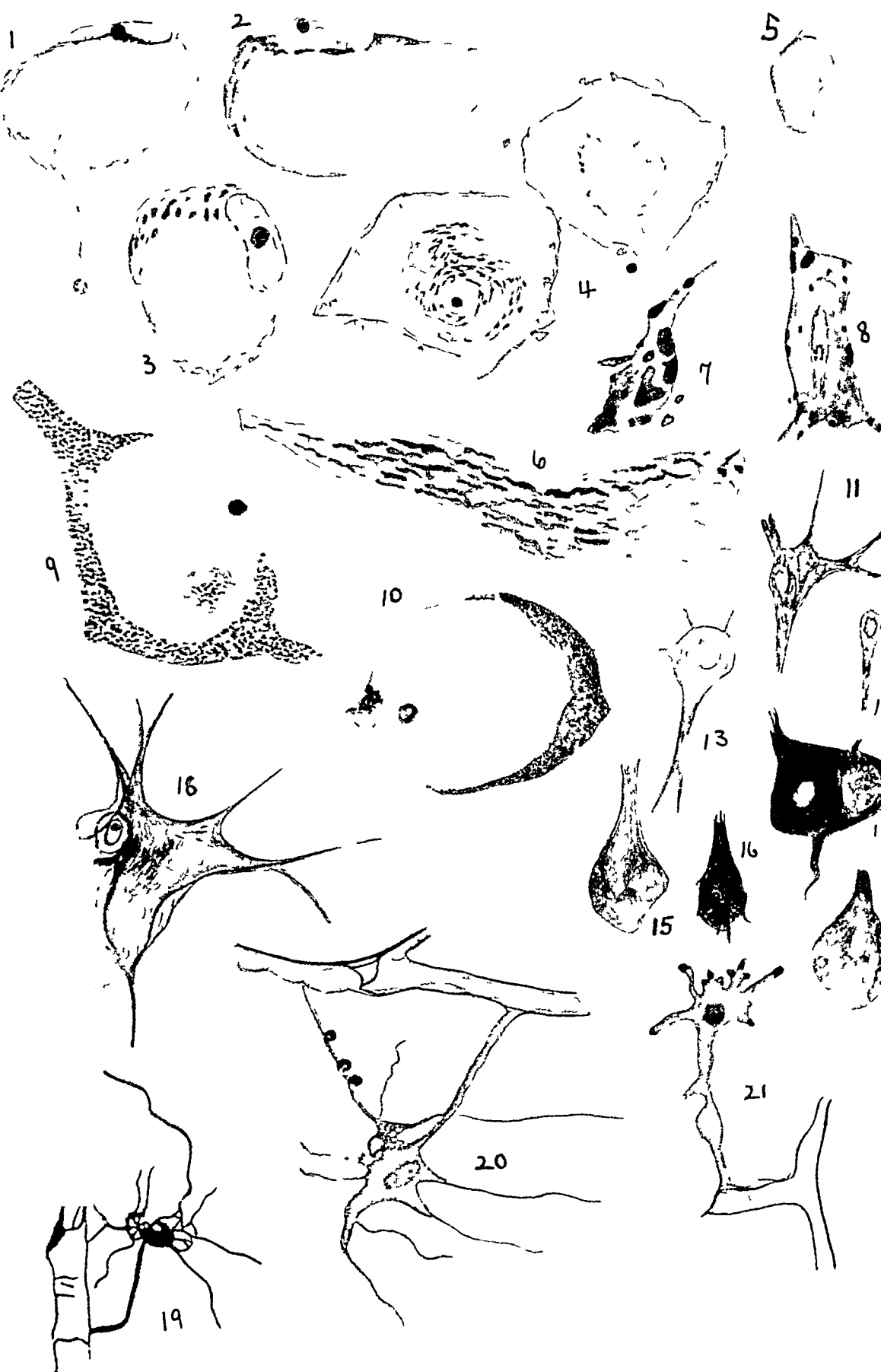
Figs 24-25 —Ameboid glia cells with coarse granulations (Alzheimer IV)

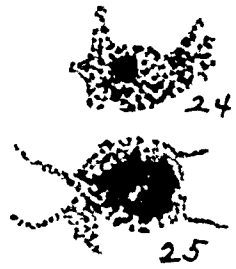
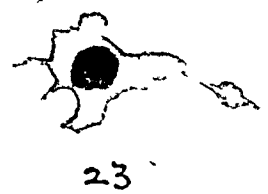
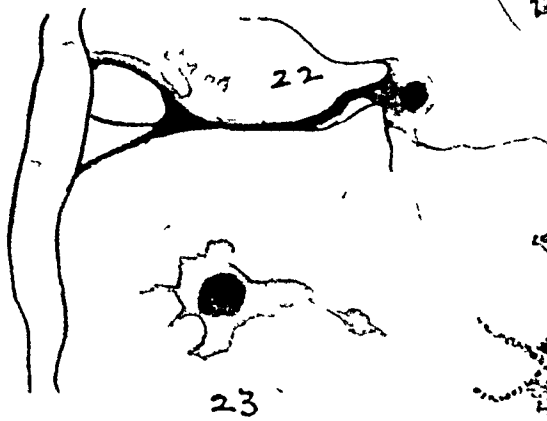
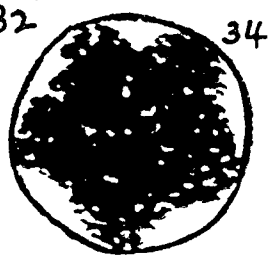
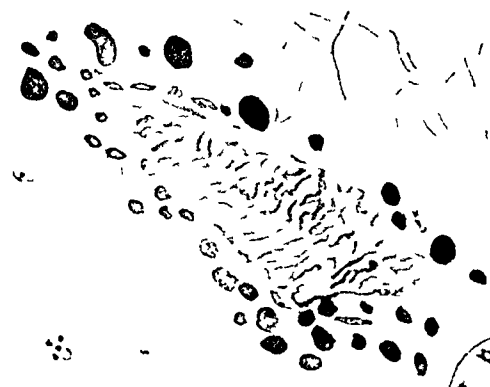
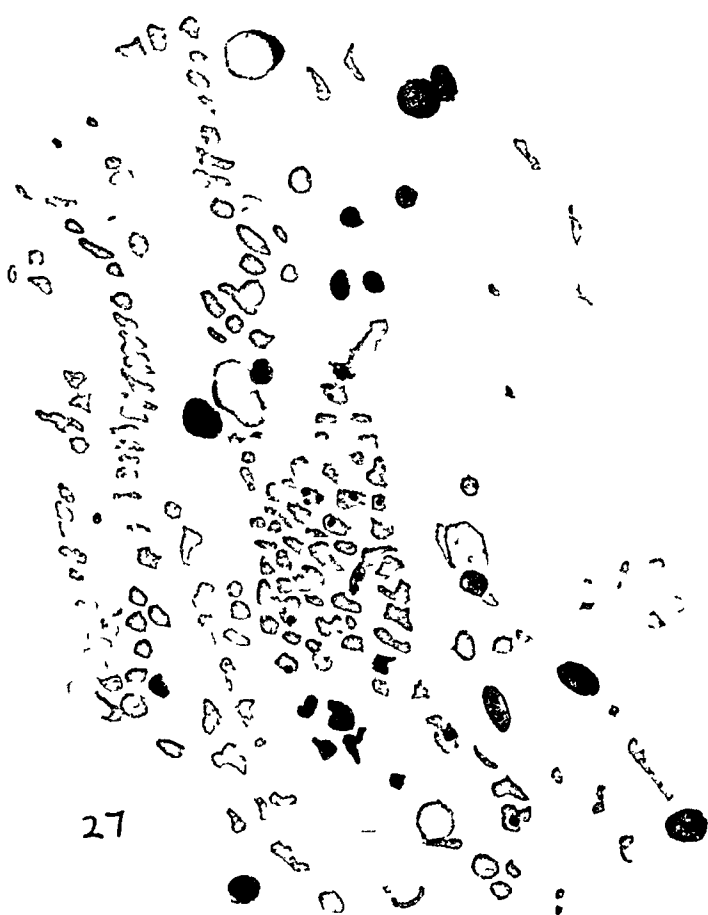
Fig 26 —Amyloid bodies about a vessel (Unna-Pappenheim)

Fig 27 —Central canal of cord showing distortion and gliosis

Figs 28-34 —Inclusion forms in muscle and adventitial cells of small vessels from Case 1 Figure 28 shows the number of these bodies under a low power Note the apparent mitotic figures in Figures 32 and 33 Figure 34 is a transverse section (Thionin)











sive study in recent times (Bielschowsky, Simchowicz, Alzheimer, Fuller and many others), and there is a strong tendency to regard them as of extreme importance in the nervous functions of the neuron. If this is correct it seems probable that a complete loss of fibrils must mean a complete loss of function and most likely an impossibility of recovery of the neuron in question. The clinical study of pellagra would make the presence of this sequence of events in this disease at least highly improbable.

It is interesting to note that, in spite of the advanced age of some of the patients studied by us, no Redlich-Fischer plaques were found and none of the Alzheimer basket-cells were encountered. Three other cases besides the one mentioned above showed senile reticular fibril distribution.

In all cases there was noted a marked paucity of processes in the larger cells which was especially striking in the specimens impregnated with silver.

*Pigmentary Degeneration* (Plate I, Figs 9, 10) — Pigmentary changes were marked in all cases, including even those of younger age. This pigment was present in all types of cell change, as well as in cells showing normal staining and formed a very prominent feature in the Betz, large pyramidal and other cells showing axonal change. The pigment stained black with osmic acid, red with scharlach and blue with nilblue sulphate. It formed large masses at the base of the cell, sometimes extending around the displaced nucleus and into the protoplasmic processes. In many of the cells, basophil and fibrinoid granules were present in the nucleus.

Pigmentary deposits of fatty character of some degree may be considered as a normal phenomenon and the amount unquestionably increases with advancing age (Marinesco and others). Nevertheless, they have been found in a child of only two years (Pilecz). They are in general, considered to be the result of a failure to remove all products of metabolism, whether this be due to faulty elimination or excessive production. Some have regarded them as the result of degeneration of the chromatin material of the cell (Babes). There can be no question that in the cases studied here they are of pathological extent, far exceeding the amount in which present even at an advanced age. This change in the nerve cells of pellagrins has been emphasized by many authors notably Kozowsky.

5 *Nerve Fibers* — With the *Marchi stain* the brains showed diffuse scattered degeneration of radial fibers in the cortex, but none was found in the supraradial or tangential fibers. Nowhere did they form definite bundles.

In the spinal cord a few scattered, degenerated fibers were present in all regions, not in any way systemic, involving perhaps to the greatest extent the posterior columns, and especially the subpial fibers in two cases. The crossed pyramidal tracts did not seem to be more affected than the other regions and in some cases were practically free.

The anterior and posterior roots showed a few degenerated fibers, sometimes more marked in the cervical, sometimes in the lumbar region. In two cases the number of blackened fibers was quite marked.

It is somewhat striking that the pyramidal tracts show so little Marchi degeneration in view of the extremely widespread axonal change in the Betz cells of the cortex. This is especially important because the axonal changes are considered, as described above, to be the consequence of damage to the axone. Under this hypothesis one can only assume that the damage has not been sufficiently intense in most neurons, to cause degeneration of the nerve fiber, while yet enough to produce tigriolysis. On the other hand, it would perhaps be well to bear in mind that similar changes in the cell may conceivably arise in other ways, as, for instance, has been demonstrated by Wallington, in anterior cornual cells, as the result of section of the dorsal roots. In the cases here studied the former explanation has been considered the more probable, especially in the light of the recovery of the Betz cells seen in the interval cases.

*Wolters-Kultschitzky Method*—In the cortex we attach no significance to the fact that, in some cases, there was poor staining of the tangential and supraradial fibers for the reason that, in such cases, the amount of staining appeared to depend entirely on the degree of differentiation. The need for care in interpreting such findings has been emphasized by Binswanger, Nissl, Alzheimer and others. Apart from this no definite changes were found in the brain. One case showed a cerebellar atrophy with defect in staining which can have no relation to pellagra.

In the cord all cases showed some loss of staining in Goll's column which was situated in most instances in the center of the column bordering the middle line. In a few it extended forward to the commissure, and in some involved fibers scattered throughout the whole column. Under a high power the degeneration was seen to affect quite scattered fibers, the majority being well stained, and from its situation it would appear to involve the endogenous fibers belonging to the septo-marginal area and those of the cornu-commissural zone rather than the main ascending tract.

In most cases this change in Goll's column was most marked in the cervical and might be entirely absent in the lumbar and lower dorsal region. In one case it was more marked in the dorsal than the cervical region. In two it extended up to the medulla. In two cases similar pale

staining was found in the crossed pyramidal tracts, in three in Lissauer's tract, in one in the lateral basis bundle, and in two in the lateral limiting layer of Flechsig

The fiber degenerations in pellagia have been studied by numerous authors, notably Tuczek, Marie and Lombroso. The older authors claimed to find definite systemic degeneration, generally a combined postero-lateral sclerosis. Later work, however (Spiller and Anderson, et al.), seems to show clearly that systemic degenerations are certainly exceptional, and, as will be seen in the cases we have studied, they are not present.

6 *Amyloid Bodies and Pigment Granules*—An excess of amyloid bodies is present in all cases and has attracted the attention of many writers. In many of our specimens they are present in very large numbers, both in the brain and in the spinal cord. They occur beneath the ependyma, along the vessels, in the thickened glia of the most superficial layers of the cortex and periphery of the spinal cord and also around the central canal. The origin of these bodies has been much discussed. According to the older views they represent degenerated axis cylinders or myelin sheaths (Siegeit, Wolf and others) or glia cells (Obersteiner, Redlich and others). Obersteiner suggests that they are degenerative products occurring within the glia cell body which are at first surrounded by a layer of fat, and that when the cell undergoes disintegration these bodies are set free and the fatty envelope is dissolved. Recently, Alzheimer has suggested that they do not exist in the solid form during life, but are the result of precipitation of certain material from the tissue juices by the fixing fluids. Their meaning is not by any means clear, but they occur especially in chronic degenerative conditions such as the senium, etc.

The pigmentary degenerations of nerve cells have already been discussed and it is only necessary here to mention the presence of free pigment granules of fatty and fibrinoid nature in the tissues and perivascular lymph-spaces in all cases. In five of our cases there were also present granules taking a basic stain. These various granules, specially studied by Alzheimer, are found in all chronic degenerative conditions.

#### SUMMARY

There is present in the acute attack of pellagia and in the interval cases a picture compounded of acute and chronic types of reaction. The acute changes include direct and indirect chromatolysis of nerve cells, satellitosis, astrocytosis and the presence of ameboid glia cells. Under this heading would also come a very moderate amount of perivascular infiltration which indicates general intoxication.

The perivascular infiltration of the acute attack is not more marked than that found in the interval cases. This might be used as a further argument against an acute local infection of the nervous system during the acute outbreak of the disease.

The chronic changes include fatty and fibrinoid degenerations, chronic Nissl changes of the nerve cells, increase of glia fibers, regressive changes of the glia cells, permanent destruction of nerve fibers and a marked increase of amyloid bodies. Chronic vascular changes were found only in cases of chronic alcoholism and senility.

In addition to these changes, especial emphasis should be laid on the constant presence in all cases examined where death had ensued during or soon after an acute attack of pellagra, of the reaction known as central neuritis. Furthermore, this type of change was found to have almost entirely disappeared in two patients dying eighteen months after an attack, while still definitely present, though in mild degree, in a third patient dying three and one-half months after such an attack.

It would therefore appear that the acute attack of pellagra is often, if not always, accompanied by some general intoxication of special kind which disappears in some, if not all, cases in which recovery occurs. It must not be forgotten, however, that a similar reaction is found in diseases other than pellagra.

#### CONCLUSIONS

1 The acute pellagra attack is accompanied by evidence of both acute and more chronic intoxication.

2 In common with other intoxicative conditions, the acute pellagra attack gives rise to a "central neuritis" reaction.

3 None of the changes are characteristic of this particular form of intoxication.

4 There is no evidence of a local infection of the nervous system with micro-organisms.

5 From our cases it is impossible to determine whether the more chronic changes found in the absence of a recent pellagrous exacerbation belong to the pellagra picture.

6 There is no evidence to show that chronic vascular changes are essential to the picture of pellagra.

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# BLOOD-PRESSURE VARIATIONS AS INFLUENCED BY RAPID CHANGES IN ALTITUDE A STUDY OF 100 NORMAL MEN

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In view of the fact that doctors practicing at moderately high altitudes are being told repeatedly by their patients that they must leave the country on account of their health and the influence the altitude has on their condition, a series of readings was taken to see if a change of from 1,400 to 1,700 feet would be of any importance on the blood-pressure

The Homestake Mining Company, through whose courtesy this work was carried on, is a gold mining concern whose underground workings are naturally ventilated This is accomplished by having shafts in different gulches, widely separated from each other, the current of air in some of them being downward, in others upward The mine is quite free from gases because the character of the rock does not generate any *per se* A small amount of carbon dioxide is present, due to the decomposition of dynamite, the burning of candles and acetylene lamps, and the exhalations of the miners At the surface the humidity is very slight, while in the mine the air is practically saturated

The elevation of Lead, South Dakota (pronounced Leed) is 5,250 feet above sea level The shaft is 1,700 feet deep, having an altitude at its bottom of 3,550 feet

The following table shows the barometric pressure at the different locations cited in this article

Place	Altitude Above the Sea Feet	Approximate Mean Barometric Pressure	
		Inches	Millimeters
Sea level	0	30	760
Lead, So Dakota	5250	24 55	622
1700 foot level	3550	26 20	663

There is thus a difference of 1 65 inches barometric pressure between the top and the bottom of the mine

The readings were taken on the miners of this company as they were preparing to go down the shaft to work and again as soon as the bottom was reached Again, the readings were taken at the bottom after a day's work and then at the top as soon as the ascent had been made To make the descent the men stood on a cage or elevator and went down 1,700 feet in approximately two minutes Coming up, the journey was more rapid, only one minute being necessary No attempt was made to pick out

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\* Submitted for publication March 27, 1913

special men, for they were taken just as they came. They were of all ages and conditions and represent eight nationalities — Americans, English, French, Austrians, Finns, Germans, Italians and Scandinavians. No attempt was made to find out the history of previous diseases. These men were so healthy that they were able to carry on manual labor for eight hours each day, and none seemed to be worn out after the day's work.

All readings were taken in the standing position, the only practical way under the circumstances. The instrument used was a standard mercury sphygmomanometer with a 5-inch cuff placed above the elbow.

As stated above, the altitude at the top is 5,250 feet, at the bottom 3,550 feet.

The 100 men were divided as to ages as follows:

20 to 30	51
31 to 40	31
41 to 50	13
51 to 60	5

The average age is 32.42 years.

The following readings were taken (systolic):

Descending		Ascending	
Average at surface	146.45 mm	Average at bottom	145.27 mm
Average at bottom	141.07 mm	Average at surface	139.94 mm

The average pressure, according to decades, was as follows:

20 to 30 years 51 men			
Descending		Ascending	
Average at surface	145.33 mm	Average at bottom	144.19 mm
Average at bottom	139.31 mm	Average at surface	138.43 mm
31 to 40 years 31 men			
Descending		Ascending	
Average at surface	144.28 mm	Average at bottom	141.25 mm
Average at bottom	138.96 mm	Average at surface	137.35 mm
41 to 50 years 13 men			
Descending		Ascending	
Average at surface	150.30 mm	Average at bottom	156.61 mm
Average at bottom	150.77 mm	Average at surface	159.23 mm
51 to 60 years 5 men			
Descending		Ascending	
Average at surface	157.60 mm	Average at bottom	152.00 mm
Average at bottom	146.40 mm	Average at surface	147.60 mm

#### MAXIMUM PRESSURE BY DECADES

	Descending		Ascending	
	Top	Bottom	Bottom	Top
20 to 30 years	198	204	186	194
31 to 40 years	210	202	190	172
41 to 50 years*	222	226	208	208
51 to 60 years	210	184	170	166

#### MINIMUM PRESSURE BY DECADES

	Descending		Ascending	
	Top	Bottom	Bottom	Top
20 to 30 years	112	105	116	116
31 to 40 years	126	116	110	102
41 to 50 years*	222	226	208	208
51 to 60 years	136	120	116	110

\*Immediately after this reading this man developed marked signs of pulmonary tuberculosis and is now unable to work on that account.



## THE GREATEST VARIATION

Age	Descending		Age	Ascending	
	Top	Bottom		Bottom	Top
35	121	to 142	40	120	to 150
37	142	to 110	26	208	to 178

## VARIATIONS FOR 100 MEN

Descending		Ascending	
Blood-pressure increased	27	Blood-pressure increased	24
Blood-pressure decreased	61	Blood-pressure decreased	65
Blood-pressure, no change	13	Blood-pressure, no change	11
Number of men whose blood-pressure increased both up and down			10
Number of men whose blood-pressure decreased both up and down			43
Number of men whose blood-pressure remained the same either way			3
Number of men whose blood-pressure was variable			44

It is of interest to compare our readings on the surface before descending with those of Thayer's for normal cases

	Thayer's Cases	Our Cases	Difference
20 to 30 years	136 9	145 33	8 43
30 to 40 years	140 8	144 28	3 48
40 to 50 years	142 2	150 30	8 10
50 to 60 years	154 8	157 60	2 80

## CONCLUSIONS

The rapid change in altitude, either up or down, was responsible for a fall in blood-pressure of approximately 5 mm

Lower readings were obtained from the decade from 30 to 40 than from 20 to 30

It was impossible to forecast by a man's build or any other factor what influence the ride would have on his blood-pressure

It was demonstrated that after a day's work 1,700 feet below the surface the average blood-pressure was about the same as on the surface before starting to work

It was demonstrated that abnormally high blood-pressure was not a contra-indication to hard work under ground

Admitting that the standing position is responsible for an increase of from 4 to 8 mm, these readings show that there is little difference between sea level readings (Thayer's) and those taken a mile above the sea

As factors influencing some of these higher readings, there must be taken into account the facts that the readings were taken in the standing position, that the men were, for the most part, heavy users of tobacco, tea and coffee, and moderate users of alcoholic beverages. Only one or two men seemed to be nervous at the time of the examinations

## SUPERPERMEABILITY IN NEPHRITIS \*

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In a series of studies of renal function in the various clinical types of nephritis undertaken this year, I have been impressed by a striking peculiarity in the behavior to the functional tests of four cases,<sup>1</sup> all of which, clinically and from the urine examination, apparently belong to one group. The one feature characteristic to all has been a supranormal excretion of the substances employed in the functional tests in the presence of undoubted and severe renal disturbance.

In this connection it is interesting to note the recent article by Pepper and Austin,<sup>2</sup> in which these authors describe a case apparently of the same character as those here reported. The case cited was undoubtedly an instance of parenchymatous nephritis in which the phthalein test on one occasion showed an excretion of 71 per cent for two hours, and two months later, 82 per cent for the same time. There was, however, evidence of definite impairment of the chlorid elimination which has also been true in our series.

In our observations we have also studied the fluid balance, the elimination of lactose and potassium iodid (as described by Schlayer<sup>3</sup>) and the percentage of rest nitrogen in the blood-serum. The general response of these patients to all of the tests was essentially the same, and indicated in each instance, a condition of increased, rather than diminished permeability of the kidney, except as to the elimination of sodium chlorid. In spite of this apparently normal function there were other evidences of a severe grade of renal injury of the parenchymatous type.

It is unnecessary at this time to describe in detail the methods used in carrying out these tests, as they were in general similar to those described by Rowntree and Fitz<sup>4</sup> in their recent paper. Briefly, they were performed as follows:

**Phthalein Test** According to the intramuscular technic of the original authors.<sup>5</sup>

**Lactose Test** 2.5 gms of lactose were dissolved in 25 c.c. of distilled water, pasteurized for four hours on four successive days and then injected intravenously.

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\*From the Chemical Division of the Medical Clinic.

\*Submitted for publication April 29, 1913.

1 These cases form a part of the whole group which will be reported in detail later.

2 Pepper and Austin. *Am Jour Med Sc*, February, 1913, p. 254.

3 Schlayer. *Deutsche Arch f klin Med*, Dec. 28, 1910, c1.

4 Rowntree and Fitz. *THE ARCHIVES INT MED*, 1913, 11, 258.

5 Rowntree and Geraghty. *THE ARCHIVES INT MED*, 1912, 11, 284.

The excretion of this substance was tested qualitatively with Nylander's solution and also measured quantitatively by the polariscope. The normal time for excretion is from four to five hours (Schlayer).

**Potassium Iodid Test** One half gram was given by mouth, and the urine tested by Sandow's method. The completion of excretion within sixty hours is regarded as normal (Schlayer).

**Rest Nitrogen Test** After precipitation of the proteins by alcohol, as described by Widal, the nitrogen in the filtrate was estimated by the Kjeldahl process. Normal serum so treated contains 4 to 6 gm per liter.

A short history of the individual cases might be of advantage before considering them in detail with regard to their behavior toward the functional tests.

#### CASE 1—Clinical Diagnosis Chronic Nephritis

A boy of 15 years complained of swelling of the face and legs. There was a past history of scarlet fever at the age of 2 years and some increased frequency of micturition in the past year.

His present trouble began one year before admission to the hospital with swelling of his face and legs which disappeared during the summer months and reappeared again in October, 1912.

Physical examination showed some puffiness of the eyelids and moderate edema of the ankles and feet. Otherwise the examination, including the eye grounds, Wassermann and tuberculin reactions was entirely negative.

There was a moderate anemia with 4,000,000 R. B. C. and 50 per cent Hgb (Sahli).

The blood-pressure was 150 mm (Tyco) on admission, but fell rapidly to 130.

The urine, during three weeks observation, showed constantly 7 to 12 grams of albumin per liter, with a moderate number of hyaline and granular casts, specific gravity 1.013 to 1.023, reaction acid.

There was no fever.

**Functional Renal Tests** Phthalein was excreted to the extent of 75 per cent after one hour and 85 per cent after two hours.

Lactose was detected only in specimens for the first two hours.

Potassium iodid was still being excreted after seventy-two hours.

The rest nitrogen of the serum was 33 gm per liter.

The fluid balance was normal on an intake varying from 600 cc to 1,500 cc in twenty-four hours.

**Sodium Chlorid** On an excess intake of 7 gm he excreted but 2 gm extra in the urine and gained 1½ pounds in weight in twenty-four hours.

#### CASE 2—Clinical Diagnosis Chronic Nephritis

This patient was a man of 35 years, complaining of swelling of the feet and ankles. He had had the usual infections of childhood, including scarlet fever at the age of 11 years, but without any history of sequelae. For the past year he had noticed some increased frequency of urination.

The onset of his present symptoms occurred three weeks before his admission to the hospital with nausea and vomiting, marked dyspnea on exertion and edema of the feet, which had been increasing up to the time he applied for treatment.

The physical examination showed some edema of the face and rather marked swelling of the ankles and feet. His heart was of normal size and the liver not enlarged, in short, there was no evidence of broken compensation. The eye grounds, Wassermann and tuberculin reactions were negative.

There was a moderate grade of anemia with 3,800,000 red blood cells and 60 per cent Hgb (Sahli).

The blood-pressure was 190 mm (Tyco) on admission, but fell rapidly to 140.

Cystoscopic examination was negative, phthalein appeared in seven minutes on both sides and the amount of urine was the same from each kidney, thus

excluding a unilateral lesion, possibly of a tuberculous nature, as was at first suspected. The urine during a period of two months showed 2 to 4 gm of albumin per liter, with hyaline and granular casts, and occasionally a few red blood-cells. The reaction was acid, and the specific gravity 1.010 to 1.015.

There was a persistent fever varying between 99 and 101 F for the first two weeks, after this the temperature remained normal until his discharge from the ward.

**Functional Renal Tests** Phthalein was eliminated to the extent of 45 per cent in each of the first two hours, making a two-hour total of 90 per cent.

Lactose was detected in the urine for six hours, which is generally given as the upper normal limit of time.

Potassium iodid was excreted for sixty-eight hours.

The rest nitrogen of the serum was 4 gm per liter.

The fluid balance was normal on an intake from 1,000 to 1,600 cc per day.

**Sodium Chlorid** On an excess ingestion of 7 gm only 4 gm extra were excreted, but there was no demonstrable gain in weight.

**CASE 3—Clinical Diagnosis** Bilateral pleurisy with effusion, acute arthritis, chronic nephritis.

The patient was a colored man, aged 22, who came to the hospital complaining of a cough, pain in the side, and swelling of the feet. His previous health had always been perfect until the onset of his present trouble, which began three weeks before with the symptoms enumerated above.

The physical examination revealed the presence of fluid in both pleural sacs, from which the pneumococcus was grown in pure culture. The heart was normal and the blood-pressure 115 mm (Tyco). There was edema of both feet, more on the left, due to a coexisting acute arthritis of the left ankle.

The blood count showed 3,000,000 red blood-cells and 53 per cent Hgb (Sahli).

The temperature was irregularly elevated, varying between 100 and 104 F.

Examination of the urine showed the constant presence of albumin, persisting until the patient was discharged, two weeks after the fever had subsided. The amount, however, was not large as in the other cases. The specific gravity averaged 1.015 and there were a few casts present.

**Functional Renal Tests** The phthalein test revealed an excretion of 72 per cent for the first hour and 83 per cent for two hours.

Lactose was excreted over a period of four hours.

The potassium iodid test was not done as the patient was receiving this drug medicinally.

The rest nitrogen was 18 per liter.

The fluid balance was good on an intake between 1,000 cc and 4,000 cc.

**Sodium Chlorid** On an excess intake of 7 gm, 34 gm extra were excreted in the urine and the patient gained 2½ pounds in twenty-four hours.

**CASE 4—Clinical Diagnosis** Chronic parenchymatous nephritis.

The patient, a girl aged 20, complained of swelling of the feet. Her health had always been excellent until the onset of her present symptoms, which followed an attack of so called "grip," eight months previously, after which she first noticed the edema. The persistence of this symptom was her only complaint and was likewise the only striking feature revealed by examination. Her circulatory system and blood-pressure were normal. There was no fever.

The urine, over a prolonged period, contained from 7 to 10 gm of albumin per liter, the sediment showed a few epithelial casts. Specific gravity, 1.010 to 1.020, reaction faintly acid.

**Functional Renal Tests** The phthalein test revealed an excretion of 42 per cent for the first hour and 69 per cent for two hours. The test, repeated two months later, showed 57 per cent for the first hour and again 69 per cent for two hours.

Lactose was demonstrable for but one hour. Repeated one week later, it was present for two hours, and again, two months later, it was positive for four hours. At the time of the last test the patient was definitely worse, showing a marked salt retention, with a steadily increasing edema.

Potassium iodid was excreted for forty-seven hours.

The rest nitrogen was 16 gm per liter.

The fluid balance, at the time these studies were made, was normal on an intake from 1,000 cc to 1,800 cc per day.

Sodium Chlorid. On an excess intake of 10 gm the excretion increased but 3.5 gm, and the patient gained 2 pounds in weight.

The brief outline of these cases given above will suffice to show their striking similarity, both in the clinical picture presented and in the general character of the urine. Furthermore, their behavior toward the various functional tests, particularly in the excretion of lactose and phthalein, was much the same. In all there was a remarkably good excretion of these substances in the presence of strong evidence of definite and possibly extensive renal changes.

Their similarity is further manifest in the uniform tendency toward poor elimination of sodium chlorid—a feature, also, of the case described by Pepper and Austin.<sup>2</sup>

While one would expect to find sporadic cases showing an anomalous excretion of any drug, the occurrence of four such examples in a comparatively short period of time (less than six months) would make one wonder whether this condition of such unusual permeability of the renal filter were present in a definite type of the disease, or whether it occurred at some stage in the various forms of nephritis. A third possibility, of course, would be that these cases offer only another example of the well-known hospital experience, that odd cases have a decided tendency to come in groups.

In considering the question of hyperpermeability, it must be recalled, of course, that many observers have called attention to the fact that in chronic parenchymatous nephritis the functional tests failed to give an adequate idea of the severity of the renal lesion. Bard,<sup>6</sup> and later Bard and Bonnet,<sup>7</sup> showed that the rapidity of elimination of methylene blue might be normal, or even exaggerated. Bernard<sup>8</sup> and Castaigne<sup>9</sup> also support this view, the former concluding that in the earlier stages of chronic parenchymatous nephritis, "dominated by the presence of edema and albuminuria, the renal permeability is normal, or even increased." "Later, after the disease has lasted for some time, the permeability becomes diminished." Dreyfus,<sup>10</sup> working with rosanilin, found that this dye behaved in a similar manner with regard to the rapidity of

6 Bard. *Gaz hebdomadaire de médecine*, Paris, 1897, 11, 494.

7 Bard and Bonnet. *Archives générales de médecine*, Paris, 1898, pp 129, 283, 464.

8 Bernard. *Thèse de Paris*, 1900, pp 104-147.

9 Castaigne. *Thèse de Paris*, 1900.

10 Dreyfus. *Thèse de Lyon*, 1898.

elimination, though the quantity secreted was, in his cases, less than normal. In studying the elimination of phthalein in these cases, Rowntree and Geraghty<sup>11, 5</sup> found no examples of any apparent hyperpermeability for this drug, although they were aware that it did exist for methylene blue and rosanilin. Sellards,<sup>12</sup> however, cites one case of parenchymatous nephritis in which the phthalein output was 79 per cent for two hours.

A glance at the accompanying table will suffice to show that the phthalein elimination was well above normal in three out of the four

TABLE SHOWING WATER INTAKE AND OUTPUT AND THE EXCRETION OF VARIOUS SUBSTANCES  
AUTHOR'S CASES

	NaCl added to diet, Gm	Water		NaCl Gm	Lactose	KI	Phthalein, Per cent			N P
		Intake	Output				1st hr	2d hr	Total	
Case 1	7	*780 *600	525 890	27 46	2 hrs	72 hrs +	75	10	85	
Case 2	7	1375 2420	825 1250	43 81	6 hrs	68 hrs	45	45	90	
Case 3	7		1000 650	6 94	4 hrs	Not given	72	11	83	
Case 4	7	1300	1250	24	1 hr	47 hrs	42	27	69	
					(1 week later) 2 hrs					
					(2 wks later) 4 hrs		(2 mos later) 57	12	69	

\*NOTE—The upper figures in each case represent the average water intake and excretion of the NaCl excretion for the several days preceding the NaCl test. The lower figures are day on which the excess NaCl was given.

cases, and, in the fourth, was certainly well within the normal limits. Two of them showed a striking excretion of 72 per cent and 75 per cent, respectively, in one hour—an excretion 20 per cent higher than was found in any of the cases of parenchymatous nephritis reported,<sup>5</sup> and 10 per cent higher than occurred in the normal cases,<sup>5</sup> in which the drug

11 Rowntree and Geraghty Jour Pharm and Exper Therap, 1910, vi, No 4, 606-607

12 Sellards Johns Hopkins Hosp Bull, October, 1912, p 298

was injected intramuscularly, as it was in these patients. The anemia present could hardly have had any influence, since it has been shown that in moderate grades there is no variation in the excretion of phthalein, whereas severe anemia tends to decrease the output.<sup>5</sup>

Rowntree and Geaghty, whose experience with the use of this test is far larger than my own, are equally at a loss to explain the supranormal excretion present in these cases, and it was at their suggestion that subcutaneous injections of tetra-chlor-phthalein (which is known not to be excreted by the normal kidney) was tried with the hope of demonstrating an increased permeability, if such were present. The test was unsuccessful, though it should be added that it was given in doses much smaller than what is now known to be the maximal amount tolerated by normal individuals without excretion in the urine.

The lactose test showed the same tendency toward an increased rapidity of excretion that was observed in the elimination of phthalein. The usual time for excretion, according to Schlayer,<sup>3</sup> is four to five hours, and occasionally six hours in rare cases. In three injections (see table) the time of excretion was well below normal, in two more it was just four hours, which is the lower limit of normal, while in only one was six hours required. This might possibly be interpreted as a slight delay. The percentage of excretion has been purposely not stated for the following reasons. In two of the early cases the total output was not determined, since Schlayer had emphasized chiefly the duration of excretion as giving the most valuable information. We have evidence, however (which will be brought out in a subsequent paper), which makes it seem probable that determinations of the total output are most essential in drawing proper conclusions from the test. Also there was some fever in two of the patients, which seems to influence the excretion, although Schlayer has apparently not found this to be the case. It might be mentioned, however, that in one test, in which the duration of excretion was only two hours, the output was 76 per cent, which, in comparison with the results in healthy people, is a good normal figure.

The results with the iodid test are most interesting. In two out of the three cases in which it was given, there was a definite delay in excretion, which, in connection with the impaired elimination of sodium chlorid, would seem to support Schlayer's view that the excretion of these two substances is the best index of tubular function. On the other hand, the excretion in the third case was complete at a time well inside the normal limit, while the NaCl elimination was similar to that in the other cases. It so happens that the subsequent course of this patient has indicated that the tubular destruction here was severer than in either of the others.

While it is true that the atypical response of a single isolated case is in no way conclusive, it gives definite evidence that the test is not infallible and adds support to the doubts as to its value, which were expressed by Rowntree and Fitz,<sup>4</sup> and in which, from experience with other cases (to be reported later), I quite concur. A possible explanation of this apparent anomaly is that in the very severe forms of tubular destruction the iodid tends to be suppressed rather than delayed.

The fluid balance and general response to increased NaCl ingestion may be appreciated from a glance at the accompanying table, and require but a word of explanation. Both factors were estimated daily until an approximate constant had been reached, and sufficient NaCl was given to avoid tissue starvation and possible chlorid retention from this cause. The tendency toward impaired salt elimination has been common to all cases and it has been the one test in these cases which gave evidence of functional renal impairment. This only serves to emphasize again the importance of determining the NaCl tolerance in edematous cases, a point which has been emphasized chiefly by Widal.

The principal features of resemblance in these cases, then, have been two

- 1 Impaired elimination of NaCl
- 2 Supranormal excretion of lactose and phthalein

While it is true that these cases do not in any sense establish the fact that increased renal permeability can exist — and this explanation should be taken only as a suggestion — the observations at least indicate that there may exist either a definite type of nephritis in which the kidney is super-permeable to some of the substances used for the functional tests, as well as to serum albumin, or that this may be merely a transitory stage in certain types of nephritis.

This report is not, in any sense, to be interpreted as a criticism of functional kidney tests, but rather to emphasize the fact, already pointed out with regard to methylene blue by Baird, Bernard and others, that there are some cases at least, and possibly more than we have hitherto believed, in which certain functional tests may give entirely normal results in the presence of outspoken and serious renal changes. It has, of course, long been known that there may exist definite anatomical lesions of the kidney without evidences of impaired function. The cases here described, however, would indicate that there may be both definite anatomical lesions, as indicated by the urinary examination, as well as definite functional impairment, as shown by the deficient NaCl elimination, without disturbance in the excretion of other substances used in functional tests. Those who have worked most in this field have all encountered cases in which these tests revealed an elimination far better than the clinical examination would have led one to suspect. In these



instances it has usually been assumed that the high excretion following the functional tests justified a good prognosis, which may, of course, be true also in this series for none of them has yet come to autopsy. It is also a well-recognized fact, clinically, that one occasionally sees a case with marked evidence of renal injury which goes on to apparently complete recovery. This question, however, only the future can decide. It is worth mentioning that two of these patients, who have been followed since, have shown no evidence, as yet, of any definite improvement in a period of three to four months.

In conclusion, it might be well to emphasize again some of the features which have been most striking in the study of these cases.

- 1 That there exist cases of well-marked nephritis with evidence of impairment of renal function in which certain tests reveal an eliminative power normal or even above normal.

- 2 That these cases may be more common than we have hitherto supposed, judging from an experience of four such examples in several months.

- 3 That the evidence from these suggests that there may exist in some types of nephritis a stage in which the kidney is hyperpermeable, at least to some substances used for functional tests, with an elective impermeability for chlorids as suggested by Widal.

- 4 That it is necessary to study renal function from the standpoint of a considerable series of functional tests rather than to draw conclusions from the excretion of any one drug.

It is a pleasure to thank Drs. Thayer and Barker for the interest taken in these cases and for allowing these studies to be made on the patients under their charge.

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# ACUTE UNILATERAL NEPHRITIS, WITH REPORT OF A CASE

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*Synopsis of Authors' Case*—Woman, aged 22 years, seized with sudden pain in the left loin, radiating forward into the left hypochondrium, rigidity of lumbar muscles with tenderness in costovertebral angle, fever, rapid pulse, leukocytosis, in urine albumin, hyaline and granular casts, red blood-cells and pus cells. Patient moderately septic, nephrectomy, kidney the seat of disseminated, suppurative nephritis. Patient made a good recovery although some weeks later it was necessary to remove the submaxillary gland for calculous inflammation.

Pathological and clinical studies have caused the belief to prevail that acute hematogenous inflammation of the kidney is always bilateral. This is, however, not the case, but exceptions to the rule are so rare and so little understood that reports of single instances are not without value. Acute unilateral inflammations differ from the commoner types of acute nephritis in that they are of an interstitial character, rather inflammatory than degenerative, and with a strong tendency to the formation of abscesses. Acute bilateral interstitial inflammation has long been known. It was found by Councilman<sup>1</sup> in scarlet fever, and has been seen in erysipelas, osteomyelitis, endocarditis, and pyemia. The infection in these cases is conveyed to the kidney by the blood-stream. Suppurative inflammation, pyelitis and pyelonephritis, is of course common in association with stone and tuberculosis. It is usually considered to be due to ascending inflammation, although this is by no means clearly established. In addition, there is a group of borderline cases, as, for instance, the pyelitis and pyelonephritis of pregnancy and the puerperium, in which it is difficult to say how the inflammation reaches the kidney. We are inclined to believe that even in these it is more likely to be hematogenous than an extension from below upward.

The particular type of unilateral nephritis to which we wish to refer in this communication is that which attacks a person apparently well, often without warning and with an unusually acute onset. In some patients the progress of the disease may be so rapid that in a few hours extreme prostration is observed, while in others the course may be protracted so that several days elapse before marked septic symptoms are noted. The patient complains of tense, throbbing pain in the loin, often radiating into the anterior aspect of the abdomen. There is tenderness

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1 Councilman, Trans. Assn. Am. Phys., 1898, viii.

over the same area, but most marked at the costovertebral angle, and this is accompanied by rigidity of all the muscles of the loin and of the oblique muscles of the abdominal wall. There is fever of variable degree with a correspondingly rapid pulse and a moderate leukocytosis. The urine is rather scanty in amount, of high color and turbid in appearance. It contains a considerable amount of albumin, and the sediment consists largely of casts, red blood-corpuscles and pus cells. Certain general manifestations such as headache, nausea and vomiting, delirium and even symptoms of uremia may appear and the patient looks and is extremely toxic.

In 1895 Weir<sup>2</sup> and Woodward<sup>3</sup> each reported cases of nephrectomy for unilateral suppurative nephritis, but the present surgical treatment of this affection is mostly due to the able teachings of Brewer,<sup>4</sup> who has persistently called attention to the subject, and in his latest contribution reports an experience of fourteen cases of the acute type and about a dozen of the mild type. Cobb<sup>5</sup> collected eight cases from the surgical wards of the Massachusetts General Hospital, all of them operated on since 1902. There are a few other instances recorded in the literature, and the number is increasing so that we shall soon become familiar with the affection and approach its diagnosis and treatment with more certainty and confidence.

#### CASE REPORT

The case that we have observed and of which we have given an epitome at the beginning of this article is as follows:

*History*—Miss R. A. K., aged 22, had measles, mumps and scarlet fever when a child. In 1909 she had a severe attack of typhoid fever complicated with hemorrhages, but convalescence was not otherwise interrupted. She was quite well during the summer of 1910. Later she was married. During the early part of December, 1910, she suffered for two weeks from general aches and pains supposedly influenzal in origin, after which a vague pain persisted in the left loin and she herself believed that some swelling was present, but her physician did not notice anything. December 23, she rode fourteen miles into the country in an automobile the day being exceedingly cold. At 3 a. m. on December 24 she awakened nauseated and had an attack of vomiting, some hours later moderate pain in the left loin set in, and there was tenderness and rigidity, the temperature rose to 102° F. and the pulse to 120. The leukocytes on this day were counted and found to be 7000, but two days later they had risen to 13000. Daily examinations of the urine were made and showed it to be highly colored and to contain albumin and casts but no pus cells. The attack gradually subsided, the pain and tenderness disappeared, but some rigidity persisted. December 30 she insisted on getting out of bed, following which all the symptoms recurred and about this time it was noticed that pus was present in the urine. We saw her first on Dec. 31, 1910, at her home in the country.

2 Weir. *Med. Rec.* New York, 1895, LV, 325.

3 Woodward. *Ann. Surg.* 1895, XXI, 588.

4 Brewer. *Surg., Gynec. and Obst.* 1906, II, 485. *Ibid.*, 1908, VII, 699, *Jour. Med. Soc. New Jersey* 1909, VI, 61. *Yale Med. Jour.* 1911, XXII, 237.

5 Cobb. *Ann. Surg.* 1908, XLIII, 680.



*Examination*—We found a well nourished, rather pale young woman, complaining of pain in the left loin and left hypochondrium, radiating at times down to the groin and sometimes to the back. Tenderness to pressure existed at the costovertebral angle and extended forward to the crest of the ilium. There was distinct rigidity of the muscles in the loin and a sense of fulness to palpation although no tumor could be detected. There was fever and a rapid pulse and a moderate leukocytosis, and urine analysis showed albumin, with hyaline and granular casts, erythrocytes and pus cells in the sediment. The patient was not particularly prostrated, although she looked somewhat septic. We made a positive diagnosis of unilateral infection of the kidney. As she was a woman with abundant vitality and energy, we believed it would be safe to temporize a few days and await developments. Accordingly, hot fomentations were ordered for the kidney region, and hexamethylenamin (urotiopin) and an abundance of water, liquid diet and purgation were prescribed. During the next ten days the patient varied in her condition, sometimes being on the verge of marked improvement, again having a relapse to the condition just mentioned. Finally, as the temperature continued around 102 F, and as her general appearance indicated an increasingly septic state, and as some delirium was manifested, an operation was deemed advisable. The symptoms were always unilateral and always located in the region of the left kidney. She was admitted to St Agnes' Hospital January 11, 1911. During the few hours before operation the temperature ranged from 100 to 102 F, the pulse from 84 to 100.

*Operation*—The operation was performed Jan 11, 1911, under ether anesthesia. The patient was placed in the usual lateral position over a kidney pillow and a curved incision was made downward and inward from near the costovertebral angle. On opening the deep fascia, the perinephric fat was found infiltrated and inflamed, bleeding with great readiness. On further exploration of the fat in the region of the kidney, an abscess was encountered containing 3 or 4 ounces of thick pus. The kidney was exposed and delivered with some difficulty and was found to be the seat of a diffuse, suppurative process. Accordingly, nephrectomy was performed and the wound packed with gauze and drained with a rubber tube. Partial closure of the wound was effected.

Examination of the specimen was made by Dr. Allen G. Ellis, Dr. John Speese and ourselves, and the examination of the pus by Dr. Randle C. Rosenberger. The reports are as follows:

*Macroscopic Description*—The kidney was about one and one half times the normal size, intensely red and congested, with purple blotches of hemorrhage beneath the capsule. Near the lower pole a ragged opening existed with evidence of necrosis at its edges. In three other places rents were found, evidently caused by trauma during operation. It was afterward discovered that at the places hemorrhagic infarction existed. On section of the kidney the entire organ was seen to be intensely congested, especially the cortical portion, and to be the seat of numerous miliar abscesses. In the lower half, a large wedge-shaped yellow area communicated with the opening before mentioned and which had probably been made at the operation. The apex of the wedge represented the apex of a pyramid. One other such area, but somewhat smaller in size, was present. At the upper pole a round, orange colored mass about 4 mm in diameter was discovered. It was thought to be tuberculosis but was found on microscopic examination to be a hypernephroma.

*Microscopic Description*—Sections show a hemorrhagic fibrinocellular exudate on the surface of the renal capsule. At several points a large amount of hemorrhage is present and exists as an infarct. The capsular vessels are dilated and a diffuse leukocytic infiltration begins beneath the capsule and extends downward through the cortex and medulla. Many of the leukocytes are of the polymorphous form. The renal epithelium shows degenerative changes and cloudy swelling with numerous cysts. The stroma in some areas is decidedly fibrous.

There was no evidence of tuberculosis in any of the sections examined by Dr Speese, Dr Ellis or ourselves. In the specimen submitted to Dr Ellis a small hypernephroma was discovered, with extensive connective tissue formation.

*Postoperative History*—The patient reacted from the shock in a few hours, afterward the temperature gradually rose until on the fourth day it was 103 F, then it slowly declined to the normal, which was reached on the sixth day after operation. The pulse remained high, rapid and weak for several days. The patient commenced to pass urine shortly after the operation and during the first twenty-four hours 17 ounces were excreted. During the second twenty-four hours 41 ounces and during the third 57 ounces were voided. The amount of urine during the first ten days after operation varied from 33 to 57 ounces, and averaged 44 ounces, and during the last ten days of her stay in the hospital, it varied from 31 to 46 ounces, and averaged 39 ounces. At first there was abundant albumin with casts, pus cells and erythrocytes, but the sediment gradually lessened and for the last week examination was negative for albumin, casts and pus. The last urinalysis showed a specific gravity of 1.010. The gauze packing was removed from the wound during the second week, but con-

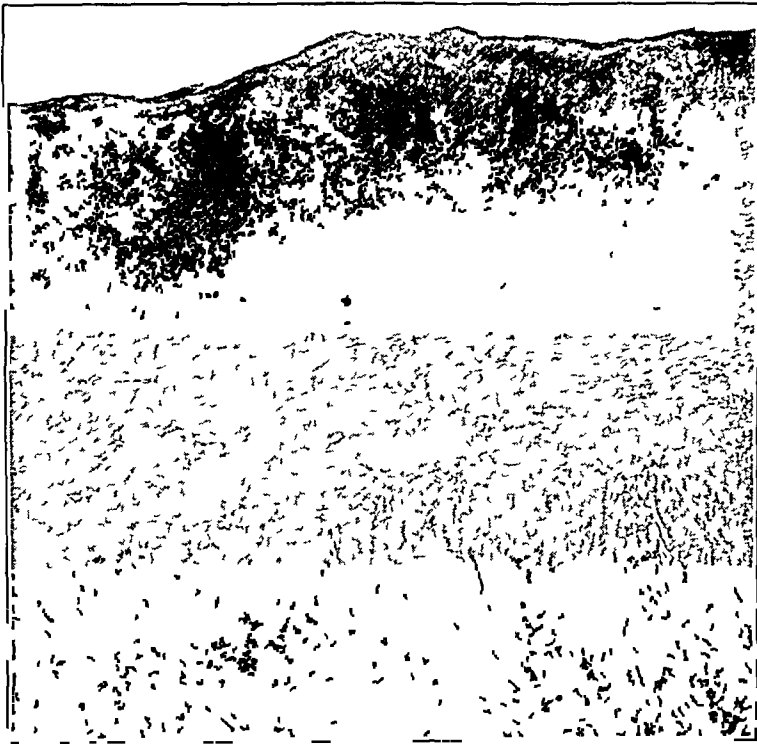


Fig. 2—Section through capsule and cortex, showing great thickening of the former, with fibroid change, hemorrhage, and round cell infiltration, pronounced cellular infiltration of superficial layers of cortex.

siderable wound trouble was experienced which protracted convalescence. A bacteriologic examination of the pus in the kidney removed at operation, and later of the wound discharge, revealed the *Micrococcus pyogenes aureus* and from the culture a vaccine was made by Dr Rosenberger and administered several times to the patient. The examination of the blood showed hemoglobin 38 per cent on the day after operation and from this it hardly varied until February 14, when it began to rise steadily. The first count of red blood cells made four days after operation revealed 3,200,000 and the count varied but little from this until February 14, when it showed 3,940,000, after which continued improvement took place. The leukocytes varied, depending on the condition of the wound, but averaged about 13,000 during her stay in the hospital.

The patient was discharged February 25, 1911, forty four days after admission, with a small sinus rapidly closing. Her general health was excellent, although some weakness persisted. The sinus healed entirely in one week. About six weeks later, the patient complained of swelling, pain and tenderness beneath the right lower jaw and noticed some salivation with a foul odor and salty taste in the mouth. An examination revealed a swelling of the right submaxillary salivary gland, densely hard in character, not acutely inflammatory but somewhat tender to pressure. Pressure caused pus to exude from the duct of Wharton into the mouth. A radiograph made by Dr. Pancoast showed the presence of a calculus.

Under ether anesthesia a 2 inch incision was made beneath the jaw and the submaxillary salivary gland removed. It contained an oval calculus about 12 mm in length. Since this time, the patient has been perfectly well, gaining in weight and strength and frequent urinalyses have shown nothing abnormal. Later she became pregnant, nothing unusual happened until October 27, when a miscarriage occurred. The patient suffered no ill effects from this, however. On November 1, she was passing 40 ounces of urine in the twenty-four hours, with a specific gravity of 1.015 and showing nothing abnormal to chemical or microscopic examination.

#### ETIOLOGY

The kidney in unilateral nephritis may become infected in one of three ways:

1 *By an Ascending or Urogenous Infection*—This is much less common than was once held, and Sampson's<sup>6</sup> well-known paper, published in 1903, states the case correctly in the following words:

The reflux of urine from the bladder into the ureters may be considered an etiologic factor in the causation and maintenance of renal infection only when the intravesical portion of the ureter is diseased, thus impairing its function, or when some ureteral abnormality exists.

It is thus seen that the kidney is protected from ascending invasion by the downward current of urine and the physical condition of the healthy ureteral orifice. Of course, infection may be transmitted to the pelvis of the kidney by an unclean ureteral catheterization.

2 *Lymphatic Infection*—A local spread of infection from the intestinal tract or from the lower urinary organs by way of the lymphatics is not common, but does sometimes occur. Some interesting experimental work has been published recently by Kunita,<sup>7</sup> showing the way in which the lymphatics of the ureter communicate with those of the perinephric tissue and kidney, and by Franke,<sup>8</sup> who found that the ascending colon and cecum were connected by a chain of lymphatics with the right kidney but was unable to find such connection in the case of the left kidney.

3 *Hematogenous Infection*—This is the common mode. It is well known that micro-organisms frequently pass through the kidney without injuring it in so far as we know. The urine swarms with typhoid bacilli in many cases of typhoid fever and one frequently observes a colon bacil-

6 Sampson. Bull. Johns Hopkins Hosp., 1903, vi, 334.

7 Quoted by Stewart. Univ. Penna. Med. Bull., 1910, xiii, 233.

8 Franke. Mitt. u. d. Grenzgeb. d. Med. u. Chin., 1911, xxii, 623.

luria, although in neither case are symptoms of kidney infection necessarily present. There has been some experimental work published indicating that the passage of micro-organisms through the kidney is always attended by damage histologically, although clinically no trouble may be appreciable. It has also long been known that by experimentally tying the ureter, bruising the kidney and injecting cultures of staphylococci into the veins, the kidneys will become infected. These infections point the way to an understanding of the workings of well-known clinical conditions as factors in the etiology of pyelonephritis. Most cases of pyelonephritis are probably unilateral in the beginning. Theoretically, a source of infection must exist somewhere in the body, although it

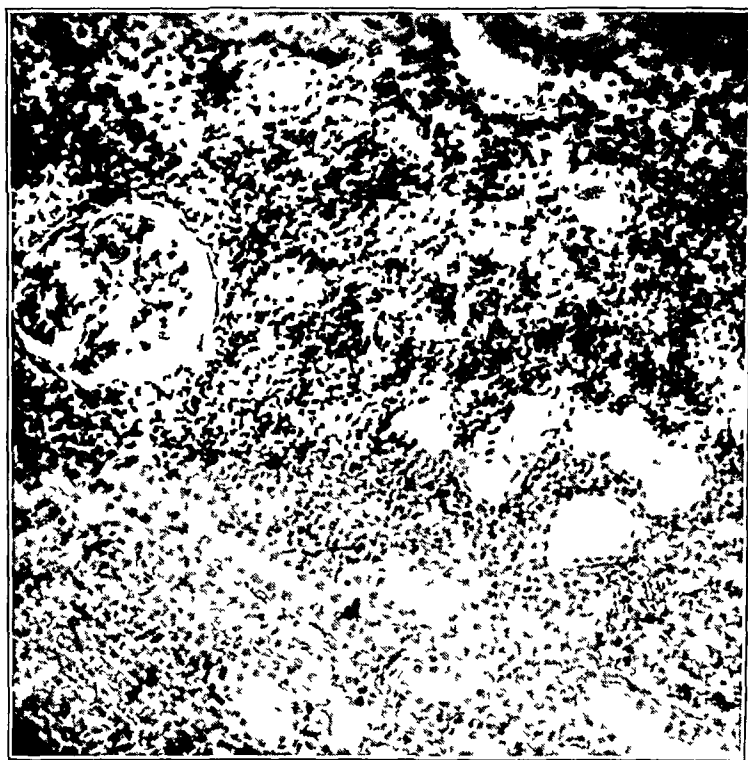


Fig. 3—Section through cortical portion of kidney showing intense intertubular and periglomerular round cell infiltration

is not always easy to ascertain the source. In view of the fact that the colon bacillus is the most frequent cause of urinary infections, we may reasonably infer that intestinal stasis, intestinal ulceration and severe and long-continued constipation act as predisposing factors. Previous infections, such as furuncle, tonsillitis, tooth abscesses or any form of peripneural suppuration may predispose to pyelonephritis. The bladder, the prostate gland and the uterus and its appendages may also act as portals of entry, and certain general conditions of which typhoid fever and influenza are the most prominent examples may contribute to haematogenous infection of the kidney.



In addition to the entrance of infection, there must be some cause traumatic or otherwise, operating to reduce the resistance of the renal tissue. This, likewise, is not always easily determined. Many of the cases reported as acute unilateral pyelonephritis with suppuration have occurred suddenly in an apparently normal kidney of persons previously well, and the infecting agent was usually the colon bacillus or the *Staphylococcus aureus*. It may be that these organisms were highly virulent or in excessive number, or it may be that some unrecognized abnormality of the kidney was present. A few years ago, Kidd<sup>9</sup> suggested that as the majority of cases occur in women and involve the right kidney, undue mobility of the organ may be a predisposing factor, and Cotton<sup>10</sup> reports two cases in which there was a definite displacement of the infected (right) kidney. The micro-organisms usually found in pyelonephritis are the *Bacillus coli communis*, *Micrococcus aureus*, *Streptococcus*, and the typhoid bacillus. The great majority of cases have occurred in women, and the only explanation would seem to be the more frequent displacement of the right kidney and the greater tendency to intestinal stasis in that sex.

Recently unilateral renal hemorrhage of apparently unknown origin and sometimes called essential hematuria has been placed in the group which we are discussing and considered to be of bacterial origin. Thus, Gaudiana<sup>11</sup> concludes that with the exception of early tuberculosis, lithiasis, neoplasms, torsion of the pedicle or Bright's disease, all cases described as hemorrhagic nephralgia are cases of unilateral nephritis and are the result of bacterial invasion of the kidney. Acute hematogenous infection is also of interest in connection with the pyelitis of pregnancy, but any discussion of this disease would occupy more space than the limit of our paper permits. Louria,<sup>12</sup> in a recent paper has given some consideration to the subject. Brewer's<sup>13</sup> conclusions regarding the etiology are important and may be quoted.

During the progress of any infectious disease a certain number of micro-organisms find their way into the blood current, many of these organisms are excreted through the kidneys. If their number is comparatively small, if their virulence is low and if the kidneys are in a healthy condition the transit of these organisms through the renal apparatus gives rise to no demonstrable lesion. If, on the other hand, the number of the organisms is large if their virulence is high or if one or both kidneys are diseased, lesions are produced which may at the onset cause an overwhelming and fatal toxemia, or may proceed more slowly to the development of any of the classical types of renal infection or suppuration. While the disease may be bilateral, in a large number of instances it is unilateral and its unilateral character is due to the fact that

9 Kidd. *Urology Surgery*, 1910.

10 Cotton. *Ann Surg*, 1911, lx, 577.

11 Gaudiana. *Folia urologica*, 1908-1909, iii, 570.

12 Louria. *New York Med Jour*, 1911, xciii, 1073.

13 Brewer. *Jour Am Med Assn*, 1911, lxi, 187.

the affected kidney has lost to some extent its normal resistance to infection, by reason of trauma, abnormal mobility, previous disease, calculous irritation, anemia, passive hyperemia, complete, incomplete or intermittent hydronephrosis. The presence in the body of a kidney damaged by trauma or disease to such an extent as to lower its normal resistance to infection is a distinct menace to the individual, in that it possesses a potential susceptibility toward even the mildest forms of blood infection. While it is possible to produce renal lesions in animals by means of the *Bacillus coli*, the *Streptococcus pyogenes*, the *Staphylococcus pyogenes aureus*, the *Bacillus typhosus*, the pneumococcus, and the pyocyaneus, in clinical cases only the first four of these organisms have been isolated.

#### PATHOLOGY

The macroscopic appearance of the kidney varies with the stage of advancement of the morbid process. At first the kidney is swollen, tense

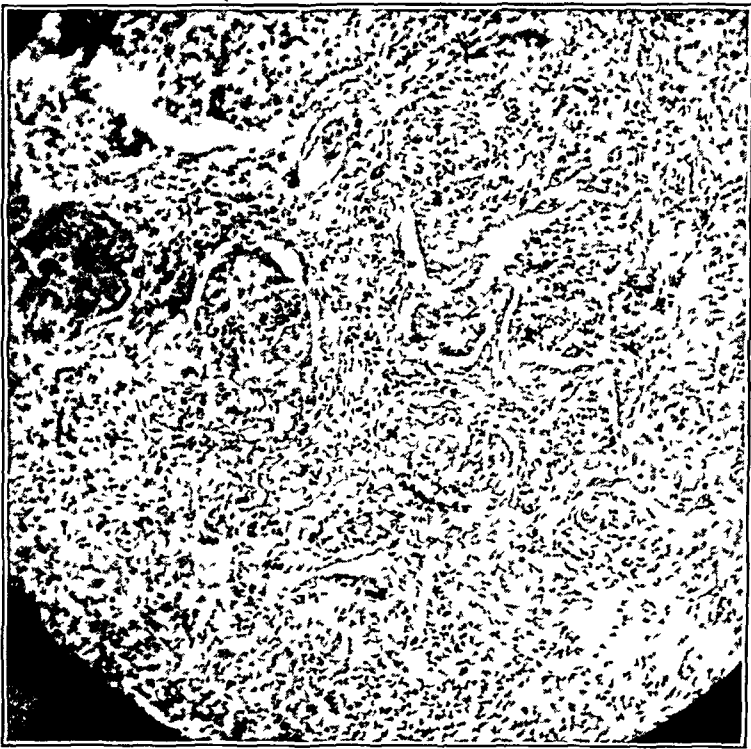


Fig 4—Section through cortical portion of kidney showing moderate amount of cell infiltration, edema, degenerative changes in glomeruli and tubules

and engorged with blood, and distinct infarcts may be seen. Later, numerous yellow nodules appear beneath the capsule surrounded by a zone of intense congestion. On section, these nodules are found to be the bases of wedge-shaped areas of suppuration in the cortex. Long linear yellow streaks may indicate suppuration in the tubules. The microscopic changes consist of a diffuse congestion and leukocytic infiltration with numerous foci of suppuration, there is often much hemorrhage beneath the capsule, and throughout the cortex triangular infarcts, hemorrhage and suppuration may be present. Large bacterial masses looking like emboli are often seen. In the later stages the foci of suppuration coalesce

and gross abscesses may be formed. The Malpighian tufts are congested and usually surrounded by leukocytic infiltration. The pelvis is congested and covered with exudate.

#### SYMPTOMS

The clinical picture of hematogenous pyelonephritis varies considerably with the virulence of the process. Brewer describes three types: 1. The severe type, in which the local symptoms are obscured by an intense toxemia, and a fatal result occurs unless the infected kidney is removed. 2. The intermediary type, with severe initial symptoms, but without grave toxemia. Renal abscess, perinephritic abscess, pyelonephritis or pyonephrosis develops in neglected cases. The symptoms may simulate appendicitis, cholecystitis, or abscess of the liver, and, if the renal disturbance is not marked, may resemble typhoid fever or pneumonia. 3. The mild type, with tenderness over the costovertebral angle as the only symptom suggesting subacute appendicitis or cholecystitis. Brewer believes that this type accounts for certain irregular periods of temperature occurring during convalescence from some surgical conditions or infectious diseases. 4. To these we will add a fourth type, that in which the chief and perhaps the only symptom is hematuria. We have referred to the observations of Gaudiani and would also add those of Eshner,<sup>14</sup> Billings,<sup>15</sup> Elliott,<sup>16</sup> and White<sup>17</sup> for additional support of the view that some of the so-called "essential hematurias" are due to bacterial invasion of the kidney.

The "severe" type of Brewer or the fulminating type of other writers is of sudden onset in a person apparently well. There is severe abdominal pain, tenderness, rigidity, nausea and vomiting. While the pain at times is characteristic of renal disease, it generally suggests some intra-peritoneal process on the side affected, usually of the stomach, gall-bladder or appendix. A number of the cases reported in the literature were operated on for appendicitis, cholecystitis or perforated duodenal ulcer before the true condition was recognized. The temperature rises sharply even as high as 106 F., and there may be a chill or succession of chills. Septic symptoms develop and sometimes death may ensue before any distinctive renal or urinary signs are observed. As a rule, however, an indication of the true condition of affairs is given by the shifting of the pain to the flank and the finding of a point of more or less severe tenderness at the costovertebral angle. It is rare that the enlarged kidney can be palpated owing to the rigidity present although some resistance may be felt by bimanual examination. The urinary findings

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14 Eshner. *Am Jour Med Sc*, April 1903.

15 Billings. *Am Jour Med Sc*, 1910, p 625.

16 Elliott. *Internat Clinics* IV 1906, 16th series p 122.

17 White. *Quart Jour Med* 1911.

during the early hours are inconclusive and do not differ from those in any other severe septic infection, but later the urine becomes scanty and contains albumin, casts, blood and pus cells and the pathogenic micro-organism in pure or mixed culture. There is usually a high degree of leukocytosis and headache, muscular twitchings, convulsions or delirium may be present. The fatal termination is due to a combination of sepsis and uremia.

The second type, the *forme argue* of Albanian, resembles the foregoing except that the intense septic symptoms are absent. More time is given in which to make a diagnosis, and the costovertebral tenderness and the urinary findings may be supplemented by ureteral catheterization. The bladder is seen to be intensely inflamed about the ureteral orifice,

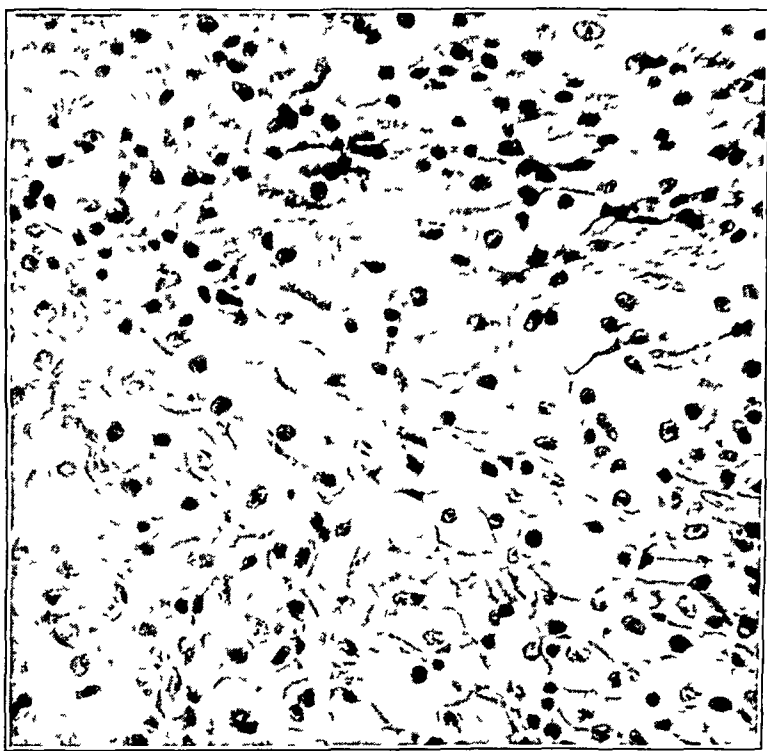


Fig 5—Section through small white nodule in cortex of kidney, showing character of the so called hypernephroma

from which pus may be seen exuding, and the lips of the orifice are edematous and pouting, and often ulcerated. The cystoscopic examination should not be undertaken during the acute attack, unless nephrectomy is contemplated. An x-ray examination should be made to determine the presence or absence of calculus.

The mild type which Brewer also terms "idiopathic pyelitis" has but few symptoms except moderate pain (backache) and costovertebral tenderness. A trace of albumin and a few casts, blood-cells and pus cells will be found in the urine. Some of these cases have no doubt been operated on for subacute appendicitis or cholecystitis, on the other hand,

they may account for "certain irregular periods of temperature occurring during convalescence from some surgical condition or infectious disease" (Brewer). The fourth type is characterized by persistent hematuria, which cystoscopy shows to come from one kidney, and the cause of which is revealed only at operation.

*Treatment*—The acute fulminating form should be operated on as soon as the diagnosis can be made with the intention of performing nephrectomy, unless nephrotomy with drainage will suffice. In 1911, Brewer reported that he had encountered fourteen cases of the severe type, two patients were untreated, and in four nephrotomy and drainage was done, they all died. Eight were treated by early nephrectomy and all recovered. The general statistics on the subject are not yet susceptible of analysis. It is quite true that the fulminating type sometimes subsides without operation, but just as in acute appendicitis, we never know which cases will recover and which will not. Of greater importance is the question of whether to do a nephrectomy or a nephrotomy. Brewer and Cobb have obtained splendid results from nephrectomy, but there is much to be said for the less radical procedure, chiefly because of the uncertainty as to the condition or even the presence of the other kidney, since there is rarely time for a cystoscopic examination. The objections that have been urged against nephrotomy are the inability to drain the whole organ by splitting it and the subsequent uselessness or even the menace of a kidney riddled with abscesses. Cases are on record in which the symptoms recurred after nephrotomy, necessitating a subsequent nephrectomy. In the subacute types, more time is given for investigation of the other kidney and the diseased organ can be more successfully treated. In the case herein reported we adopted a conservative plan of treatment for nearly three weeks, and when forced to operate we did a nephrectomy, because the friable disorganized state of the kidney forbade a nephrotomy. Of course in the mild cases operation is not to be thought of, rest in bed, a milk diet, urinary antiseptics, purgatives and plenty of water will usually bring about a cure. In refractory cases, bacterins should be used, and in persistent pyelitis it may be necessary to irrigate the renal pelvis through a ureteral catheter with a solution of one of the silver salts or with a 2 per cent solution of aluminium acetate. If still resistant, it is advisable to operate—to split the capsule and drain the renal pelvis. In all such cases the existence of pressure on the ureter or of movable kidney should be investigated.

# THE EFFECT OF URANIUM NEPHRITIS ON THE EXCRETION OF CREATININ, URIC ACID AND CHLORIDS, AND THE EFFECT OF CREATININ INJECTIONS DURING URANIUM NEPHRITIS

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## I INTRODUCTION

The experiments described in this paper were begun with the intention of determining the effect of uranium nitrate on the excretion of creatinin by the kidney, and the effect of creatinin injections on the nephritis produced by uranium nitrate. Chlorids were estimated in the last three experiments to check up the results with creatinin. Uric acid estimations were added, as it was found that no work had been done on the subject. The work was begun in the winter of 1911 during the winter's second year at the Johns Hopkins Medical School, but was not successful at that time. The experiments described below were conducted in this laboratory during the two succeeding summers of 1911 and 1912.

## II EXPERIMENTAL

*A Methods*—Dogs which had not previously been used for any experimentation were taken. They were kept in cages of the type described by Dr. Gies.<sup>1</sup> The urine was collected daily at 8.30 a. m. Powdered thymol was used as a urinary preservative. The cages were carefully cleaned each morning.

The dogs were fed on uniform quantities of hashed lean beef, cracker-meal, lard and distilled water in a homogeneous mixture. Bone ash was added to the food to insure the elimination of formed feces, which were found except when stated to the contrary in the protocols. The dogs were fed regularly at 9 a. m.

A word must be said here concerning the meat included in the diet. The amount was always small—15 grams. Closson,<sup>2</sup> Kleickner<sup>3</sup> and Lefmann<sup>4</sup> have shown that muscle as food does not increase urinary crea-

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<sup>1</sup> Submitted for publication April 9, 1913.

From the Biochemical Laboratory of Columbia University, at the College of Physicians and Surgeons, New York City.

<sup>1</sup> Gies, W. J. *Am. Jour. Physiol.* 1905, **xix**, 403.

<sup>2</sup> Closson. *Am. Jour. Physiol.* 1906, **xxi**, 252.

<sup>3</sup> Kleickner. *Bericht chem. Physiol. u. Pathol.* 1906, **v**, No. 8, p. 59.

<sup>4</sup> Lefmann. *Ztschrift f. physiol. Chem.* 1908, **liii**, 476.

tinin, and furthermore, it has been noted by Underhill and Kleiner<sup>5</sup> that there is no decrease in dogs in urinary creatinin during a fast of ten days. These observations warrant the belief that the absence of so small an amount as 15 grams of meat, during refusal of food by the animals, could not have made any difference in the output of urinary creatinin.

Intravenous injections were made from a buret through a small cannula into a saphenous vein. A very small quantity of 2 per cent cocaine solution was used as a local anesthetic.

The subcutaneous injections were made in the skin of the back or hind leg.

The creatinin was estimated by Folin's<sup>6</sup> method, the uric acid by the Folin-Shaffer<sup>7</sup> method, the chlorids by Harvey's<sup>8</sup> method, albumin with Tsuchaya's<sup>9</sup> reagent using Esbach tubes. The urines were analyzed as soon as collected.

*B Lesions Caused by Uranium Nitrate*—The acute renal lesions caused by uranium nitrate have been shown to be the same by all investigators except two. These lesions consist in general of a severe tubular injury combined with a vascular change, the latter of which has been demonstrated by physiological, but not by anatomical observations.

As to the tubular lesions, Pearce<sup>10</sup> states that "the anatomical changes due to uranium and to the chromates are in the early stages confined essentially to the tubules, especially the convoluted tubules, and consist of granular or fatty degeneration and definite necrosis often affecting large groups of tubules." This is in essence what has been found by Schlager and Takayasu,<sup>11</sup> Schlager, Hedinger and Takayasu,<sup>12</sup> Pearce, Hill and Eisenbrey,<sup>13</sup> MacNider,<sup>14</sup> Pohl,<sup>15</sup> Christian,<sup>16</sup> and Hemeke and Meyerstein.<sup>17</sup> As to the vascular changes, Clittenden and Lambert<sup>18</sup> showed as early as 1889 that uranium in its early action on the kidney caused an increased urinary volume which, when the toxic action became more decided, changed to a partial or complete stoppage of urinary secretion. Schlager states that the serious disturbances of the integrity of the renal vessels shown by functional investigation in uranium nephritis are not recog-

5 Underhill and Kleiner. *Jour Biol Chem*, 1908, iv, 165

6 Folin O. *Ztsch f physiol Chem*, 1904 xli, 223

7 Folin and Shaffer. *Ztsch f physiol Chem*, 1901, xxxii, 556

8 Harvey, E. C. *THE ARCHIVES INT MED*, 1910, vi, 12

9 Tsuchaya. *Centralbl f inn Med*, 1908 xxx, 105

10 Pearce R. M. *Harvey Lectures* 1909 and 1910

11 Schlager and Takayasu. *Deutsch Arch f klin Med*, 1910, xcvi, 17

12 Schlager, Hedinger and Takayasu. *Deutsch Arch f klin Med*, 1907, xc, 59

13 Pearce Hill and Eisenbrey. *Jour Exper Med*, 1910, xii, 196

14 MacNider. *Jour Pharmacol and Exper Therap*, 1912, iii, 423

15 Pohl. *Arch f Exper Path u Pharmacol* 1912 lxxii, 233

16 Christian Smith and Chandler. *THE ARCHIVES INT MED* 1911, viii, 168

17 Hemeke and Meyerstein. *Deutsch Arch f klin Med* 1907 xc, 101

18 Clittenden and Lambert. *Ztsch f Biol* 1889 xxi, 513

nizable from the anatomical picture. These disturbances Schlayer, Hedinger and Takayasu<sup>12</sup> showed to be an initial increase in the dilatability and contractibility of the blood-vessels of the kidney and an increased permeability followed, in a day or two, by a reversed condition (Fig 1). Pearce, Hill and Eisenbrey<sup>13</sup> confirmed this. Pohl,<sup>15</sup> working on rabbits with very small doses of uranium nitrate (0.035 mg), produced a subacute nephritis, which exhibited, physiologically, a polyuria reaching its height in a week or ten days, and showed, anatomically, at the end of two weeks, that the glomeruli were intact, but that the tubular epithelium was flattened or entirely destroyed. MacNider,<sup>14</sup> and Heineke and Meyerstein<sup>17</sup> found engorgement of the intertubular vessels and of the glomerular capillaries.

As further proof of the tubular lesion Eisenbrey,<sup>19</sup> found that phenolsulphonaphthalein is often excreted in increased amounts in the first twenty-four hours of uranium nephritis and always is excreted in

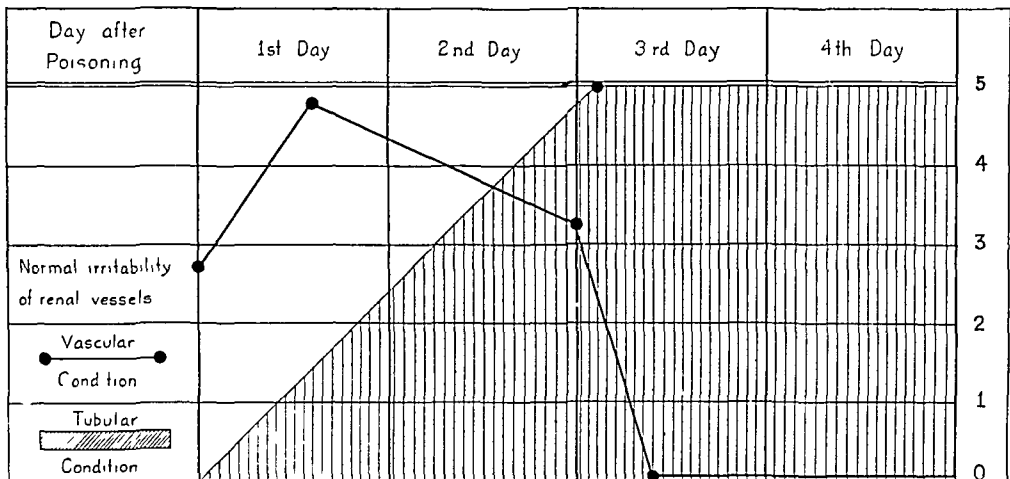


Fig 1—Effect of uranium on the kidney. 1 Faint spot like clouding. 2 More diffuse clouding and spot-like necrosis. 3 Wider areas disturbed. 4 More widely spread disturbance. 5 Practically no normal tubules remain.

decreased amounts thereafter. In view of the statement of Rowntree and Geraghty,<sup>20</sup> "that experimental evidences indicate that phenolsulphonaphthalein is excreted mostly by the tubules," the work of Eisenbrey becomes confirmatory evidence of what has been said above concerning the lesions of uranium nephritis, that is, that uranium nitrate produces a vascular reaction of one or two days' duration followed by a tubular disturbance of wide extent. Christian pointed out that in addition to the tubular lesion "there occurs in the glomeruli a degenerative condition consisting usually of the appearance of hyaline droplets of varying size in the wall of the capillary." MacNider states that similar structures have been observed in several of his experiments. He also notes that

19 Eisenbrey. *Jour. Exper. Med.*, 1911, *xiv*, 462.

20 Rowntree and Geraghty. *THE ARCHIVES INT. MED.*, 1912, *ix*, 284.



TABLE 1—CREATININ INJECTIONS AND ACUTE NEPHRITIS

Date	Weight Kilos	Temp F	Experiment 1—Diet water, 400 c c, meat, 15 gm, cracker meal, 75 gm, lard, 35 gm, bone ash, 8 gm				Feces	Remarks
			Vol, c c	Sp gr 1000	Urine— React Litmus	Creatinin, Mg		
July 21 22	8.40	101.2	250	19	Acid			
July 22 23	8.33	101.6	240	13	Acid	235		
July 23 24	8.27	101.6	275	11	Acid	203		
July 24 25	8.33	101.6	245	10	Acid	172		
July 25 26	8.25	102.0	330	10	Acid	237		
July 26 27	8.24	102.0	345	08	Acid	186		
July 27 28	8.31	102.0	305	08	Acid	265		
July 28 29	8.28	101.8	250	10	Acid	146		
July 29 30	8.36	101.8	190	14	Acid	226		
July 30 31	8.31	101.8			Acid		+	
July 31 Aug 1	8.31	101.8	285	11	Acid	190	+	
Aug 1 2	8.34	102.4	200		Acid	360	+	Feces administered
Aug 2 3	8.34	101.8	280	08	Alk	090	+	0 1056 gm creatinin injected intravenously 10 40 a m 20 c c saline
Aug 3 4	8.34	101.8	315	14	Acid	340	+	Foamy vomitus
Aug 4 5	8.24	102.4			Acid		+	
Aug 5 6	8.26	101.8	345	10	Acid	321	+	
Aug 6 7	8.30	102.0	280	10	Acid	224	+	
Aug 7 8	7.80	101.4	375	17	Acid	202	+	0 1087 gm creatinin injected intravenously 10 40 a m 20 c c saline Vomited after operation
Aug 8 9	8.15	100.8	190	25	Acid	421	—	
Aug 9 10	8.27	102.2	205	07	Acid	114	+	
Aug 10 11	8.27	102.2	300	08	Acid	216	—	
Aug 11 12	8.22	102.3	265	11	Acid	222	+	
Aug 12 13	8.20	102.2	340	10	Acid	205	+	
Aug 13 14	8.20	102.6	285	10	Acid	210	+	
Aug 14 15	8.17	102.4	275	15	Acid	317	+	0 1012 gm creatinin injected intravenously 10 10 a m 18.8 c c saline Vomited after operation Vomitus taken at 3 45 p m

Aug 15 16	8 12	102 5	290	11	Alk	234	+	Vomitus foamy only
Aug 16-17	8 20	102 5	160	10	Alk	120	+	
Aug 17-18	8 24	102 3	215	10	Alk	192	-	
Aug 18-19	8 17	102 8	312	10	Alk	243	+	
Aug 19 20	8 16	102 7	460	10	Alk	369	+	
Aug 20-21	8 16	102 5	255	07	Alk	107	+	Injected 0 1000 gm creatinin intravenously 4 30
Aug 21-22	8 23	102 4	275	11	Alk	327	+	p m 20 cc saline
Aug 22-23	8 27	102 3	235	12	Alk	105	-	
Aug 23 24	8 12	103 8	331		Alk	281	+	Slight diarrhea, 10 mg uranium subcuta 5 13 p m
Aug 24-25	7 73	102 3	681		Alk	228	-	Some food not taken
Aug 25-26	7 60	102 2	420		Acid	114	+	All food refused
Aug 26 27	7 48	100 6	*		Acid	21	+	All food refused
Aug 27-28	7 13	100 6	*		Acid	0	+	venously 4 30 p m 20 cc saline
Aug 28-29	7 02		*		Acid	0	+	Injected 0 1067 gm creatinin intra-
Aug 29 30	6 94		130		Acid	0	+	to calls
Aug 30 31	6 82	98 8	72		Acid	0	+	Apathetic, weak, does not respond
Aug 31-Sept 1	6 77	95 0	275		Acid	0†	+	All food refused Same Right eye has purulent feces bloody
								All food refused except 400 cc aq Same Left eye involved also, contractions of masseters and intercostal muscles
								Occasional spasm of fore paws Cannot stand
								All food refused Subcutaneous edema Feces bloody
								Complete spasm of fore legs a m, weaker
								not stand Feces bloody p m, dyspnea marked
								Other conditions worse Rear legs spastic now
								Died in convulsions at 3 30 p m

\* Total three days 289 cc Average each day 96 cc  
† No creatin present

different animals vary greatly in their response to the same quantity of poison per kilo. This has been found to be the case in my own experiments also.

The accompanying chart taken from the article of Schlayer and Takayasu (p. 615) shows graphically what has been stated above.

The lesions produced in my experiments, so far as concerns acute nephritic conditions aggravated by injections of creatinin, were essentially the same as those in the cases mentioned above. In the gross, the kidney was enlarged, the capsule tense, microscopically, the tubular epithelium (mainly of the convoluted tubules) was swollen, sometimes occluding the lumina, and showed granular degeneration and necrosis. The nuclei, especially in the convoluted tubules, could not be made out in most of the cells. The glomeruli were intact. Bowman's capsule was distended in many instances and the intracapsular space was partially filled with a granular material. There was no proliferation of the epithelium of the capsule. The blood-vessels were much engorged.

The kidney in Experiment 3, which was examined two weeks after uranium had been injected four times during twenty-two days, showed a somewhat different picture. Macroscopically, the kidney was swollen. The capsule was tense and not adherent. The surface was smooth. Microscopically, the lesions were mainly tubular. There were not as many injured tubules visible as in the other cases, but those which were injured seemed more severely affected. In many instances the cells had entirely separated from the basement membrane and lay as an ill-defined granular mass in the lumina. In other instances, practically normal tubular epithelium could be seen. The glomeruli showed thickening of Bowman's capsule in several instances and in a few places there was round-cell infiltration about the capsules.

*C Polyuria*—There is almost unanimity of opinion that polyuria occurs in the early stages of uranium nephritis. Chittenden and Lambert<sup>18</sup> noted it in 1889. Since then, Schlayer and Takayasu,<sup>11</sup> Pearce, Hill and Eisenbrey,<sup>13</sup> Schlayer, Hedinger and Takayasu,<sup>12</sup> and MacNider<sup>14</sup> have observed this same reaction. As stated above, this reaction has not been definitely associated with pathological lesions. The recent work of MacNider<sup>14</sup> and of Pohl<sup>15</sup> shows that with small doses of uranium nitrate, this vascular reaction may persist for more than the one or two days stated by the investigators named above.

It is interesting to note that MacNider<sup>14</sup> differentiates between anuric and polyuric animals and states that, though the vascular lesions are identical in these two groups, the tubular involvement differs markedly. In the anuric group this consists in swollen epithelium which occludes the tubular lumina, while in the polyuric group no epithelial involvement is present.

TABLE 2—ACUTE NEPHRITIS AND CREATININ INJECTIONS

Experiment 2—Diet water, 500 c c, meat, 15 gm, cracker-meal, 75 gm, lard, 35 gm, bone ash, 8 gm

Date	Weight, Kilos	Urine						Feces	Remarks	
		Vol c c	Sp 10 vx	Gr	Reac- tion, Litmus	Creat- inin, Mg	Uric Acid, Mg			Chlo- rids Gm
July 23-24	8 82	460	05		Ac	210	15	0 276	T	5 gm NaCl per os from this date on
July 24-25		415	05		Ac	170	20	0 249	T	
July 25-26	8 90	445	12		Amph	195	23	3 160	T	
July 26-27		380	13		Amph	185	29	4 710	T	
July 27-28	9 00	435	14		Amph	187	25	3 603	1 75	8 5 mg uranium nitrate, subcut 1 p m Vomit us frothy only Vomit us mixed with urine Dog refused food henceforth, 500 c c water offered Vomited most at once Amount retained (calculated) 100 c c Retained amount 125 c c 110 gm creat- inin injected intravenously 5 p m 30 c c saline
July 28-29		650	16		*	187	33	8 190	2 5	
July 29-30	7 60	850	17		*	065	123	11 390	*	
July 30-31		525	12		*	123	42	7 870	*	
July 31-Aug 1	7 23	200	06		*	086	19	11 100	*	Retained 20 c c Fine tremor Retained 20 c c Fine tremor, apathetic and weak Retained 150 c c Fine tremor Weaker, easily pushed over Retained 15 c c Fine tremor Weaker, easily pushed over Retained 10 c c Coarse tremor Can scarcely stand Nasal injection Clonic spasm of fore paws on percussion over scapular muscles
Aug 1-2		160	13		Ac	088	08	2 930	2 0	
Aug 2-3	6 90	67	13		Amph	054	08	0 970	2 0	
Aug 3-4		37	17		Ac	039	09	1 160	4 1	
Aug 4-5	6 66	67	20		Ac	073	22	0 201	1 5	Retained 10 c c Coarse tremor Can scarcely stand Nasal injection Clonic spasm of fore paws on percussion over scapular muscles
Aug 5-6		50	18		Ac	053	09		0 4	
Aug 6-7	Dog dead									

\* Vomitus admixed

TABLE 3 —ACUTE AND SUBACUTE NEPHRITIS CREATININ INJECTIONS

Experiment 3 —Diet water, 700 c c , meat, 15 gm , cracker-meal, 125 gm , lard, 50 gm , bone ash, 13 gm

Date	Weight, Kilos	Urine						Feces	Remarks	
		Vol cc	Sp 10 \	Gr \\	Reac- tion to Litmus	Creat- inin, Mg	Uric Acid Mg			Chlo- rids, Gm
July 16-17	9 30	310	06		Ac	166	11	0 155	T	+
July 17-18		260	06		Ac	152	10	0 156	T	—
July 18 19	9 35	465	07		Ac	279	20	0 372	T	+
July 19 20		330	06		Ac	198	11	0 198	T	+
July 20 21	9 30	380	09		Ac	151	14	0 228		—
July 21 22		370	07		Ac	232	15	0 222	T	+
July 22-23	9 35	410	07		Ac	258	17	0 164	T	+
July 23 24		285	11		Ac	169	18	0 215	1 0	+
July 24-25	9 25	515	12		Ac	174	27	0 309	1 5	+
July 25-26		190	13		Ac	74	10	0 414	1 5	+
July 26-27	8 85	325	06		Ac	92	28	0 065	T	+
July 27 28		150			Ac		23	0 300		+
July 28 29	9 30	445	09		Ac	220	23	0 356	T	+
July 29 30		450	10		Ac	226	28	0 630	T	+
July 30 31	9 15	390	10		Ac	252	44	1 014	T	+
July 31-Aug 1		410	10		Ac	200	23	0 902	T	+
Aug 1 2	9 00	340	10		Ac	158	19	0 816	T	+
Aug 2 3		420	10		Ac	211	26	0 840	T	+
Aug 3 4		415	10		Ac	212	27	0 747	0 5	+
										8 mg uranum nitrate subcuta 12 noon
										7 mg uranum nitrate subcuta 10 a m
										Urine lost in part
										7 5 mg uranum nitrate injected sub- cutaneously 5 50 p m
										20 mg uranum nitrate injected subcu- taneously 5 p m

8 mg uranum nitrate subcuta 12 noon  
7 mg uranum nitrate subcuta 10 a m

Urine lost in part

7 5 mg uranum nitrate injected sub-  
cutaneously 5 50 p m20 mg uranum nitrate injected subcu-  
taneously 5 p m

Aug 4-5	9 00	150	17	Alk	99	18	0 075	1 75	+	Fecal mixture, no diarrhea
Aug 5 6		480	11	Ac	193	58	0 192	0 5	+	
Aug 6-7	8 90	355	15	Ac	197	30	0 177	1 0	+	
Aug 7-8		330	13	Ac	187	45	0 231	1 0	+	25 mg uranium nitrate subcutaneously
Aug 8 9	8 95	335	14	Ac	231	36	0 435	1 0	+	4 30 p m
Aug 9-10		400	13	Ac	148	56	0 640	1 0	+	
Aug 10-11		260	20	Ac	152	49	0 416	1 0	+	Fecal mixture, no diarrhea
Aug 11-12	9 00	230	20	Alk	130	26	0 345	1 0	+	
Aug 12-13		305	13	Ac	140	29	0 884	0 5	+	91 mg creatinin injected intravenously
Aug 13 14		435	11	Ac	241	26	1 174	0 5	+	5 p m 30 c c saline
Aug 14-15	8 95	325	12	Ac	187	29	0 910	0 5	+	
Aug 15-16		280	14	Ac	153	25	0 840	1 0	+	
Aug 16-17		260	12	Ac	128	15	0 806	1 0	+	
Aug 17-18	9 00	300	13	Ac	156	23	0 750	1 0	+	
Aug 18-19		225	14	Ac	136	29	0 562	0 5	+	Fecal mixture, no diarrhea
Aug 19-20		255	13	Alk	96	22	0 612	0 75	+	
Aug 20 21	8 95	340	10	Ac	122	27	0 544	0 5	+	
Aug 21-22		415	11	Ac	182	31	0 830	0 5	+	70 mg creatinin injected intravenously
Aug 22 23		180	08	Ac	100	19	0 396	0 5	+	4 31 p m 30 c c saline
Aug 23-24	8 95	330	10	Ac	142	23	1 528	0 5	+	
Aug 24-25		290	12	Ac	77	26	0 464	0 5	+	
Aug 25 26		230	10	Ac	99	20	0 506	0 5	+	

TABLE 4—ACUTE NEPHRITIS AND CREAENIN INJECTION

Date	Weight, Kilos	Diet	Urine					Feces	Remarks		
			Vol cc	Reac- tion to Litmus	Sp Gr	Creat- inin, Mg	Chlo- rids, Gm			Uric Acid, Mg	Albu- min, Gm
Aug 8 9	14 0	water, 700 cc, meat, 15 gm, cracker meal, 125 gm, bone ash, 15 gm	480	Amph	12	284	1 594	28	T	+	30 mg uranium nitrate injected subcutaneously 11 30 a m
Aug 9 10			470	Amph	07	272	1 598	32	T	+	
Aug 10 11			450	Amph	08	185	1 495	27	T	+	
Aug 11-12	14 0		525	Amph	08	291	1 365	31	T	+	
Aug 12 13			130	Ac	20	172	1 300	43	0 5	+	
Aug 13 14			600	Ac	16	302	2 040	34	2 5	+	Vomitus mixed with urine Vomitus mixed with urine Vomitus mixed with urine Vomitus mixed with urine 0 1835 gm creatinin injected intravenously 5 p m 30 cc saline
Aug 14 15	13 10		650	Alk	20	280	0 390	56	4 5	+	
Aug 15 16			380	Alk	21	170	0 532	34	5 0	+	
Aug 16 17			285	Ac	18	90	0 342	17	2 0	+	
Aug 17 18	13 30		400	Ac	10	83	0 960	36	1 0	+	
Aug 18 19			160	Ac	10	50	0 736	09	1 0	+	Vomitus mixed with urine Vomitus mixed with urine Vomitus mixed with urine Vomitus mixed with urine
Aug 19 20			70	Ac	07	11	0 196	17	0	+	
Aug 20 21	14 10		212	Ac	10	36	0 805	14	0	+	
Aug 21-22			315	Ac	07	94	0 882	19	0	+	
Aug 22-23			545	Ac	06	117	1 417	34	0	+	Vomitus mixed with urine
Aug 23 24	13 20		850	Ac	08	161	1 700	37	0	+	
Aug 24 25			840	Ac	08	184	2 688	44	0	+	
Aug 25 26			270	Ac	09	202			0	+	

The figures in the accompanying table (Table 5) indicate that polyuria was obtained in all cases. As to anuria, this was not clearly observed in any case, due to the necessity of proceeding promptly with further injections.

TABLE 5—POLYURIA

Experiment	Vol in c c			
	1	2	3	4
Average normal	266	425	360	431
Maximum normal	345	460	465	525
Uranium nitrate nephritis	331	435	285	130
	681	650	515	600
	420	850	190	650*
		525	325	

\* Vomitus admixed

*D Chlorids*—The excretion of chlorids has been carefully investigated by Schlayer and his associates as well as by Austin and Eisenbrey.<sup>21</sup> These authors found a decrease in the excretion of chlorids. Mosenthal<sup>22</sup> has found that the excretion of chlorids may be increased, normal in amount or diminished at times, according to the conduction of the experimental nephritis. It has also been stated by Pohl,<sup>15</sup> and Austin and Eisenbrey that there is an initial increase coincident with the polyuria, after which the excretion of chlorids decreases. This was found to be the case in Experiment 4. The results of the other experiments are inconclusive.

*E Uric Acid*—The question of uric acid excretion in uranium nephritis, acute or subacute, does not seem to have attracted the attention of investigators up to now, for no references have been found in the literature. Table 6 presents some results in this connection.

From the data in this table (Table 6) we may conclude that uranium nitrate nephritis causes an increase in the amount of endogenous uric acid in the urine, that in the subacute form the excretion remains high.

*F. Creatinin*—It appears that the elimination of creatinin in acute uranium nephritis has not been studied. It is, however, interesting to note that in potassium chromate nephritis—a tubular form—Levene and Kristeller,<sup>23</sup> and Lefmann<sup>4</sup> found a decrease in the excretion of creatinin. J. L. Green<sup>24</sup> notes that “creatinin was slightly reduced,” but his results are by no means conclusive. Table 7 shows the results for acute uranium nephritis.

In subacute nephritis the amount of creatinin excreted is reduced. The protocol of Experiment 3 shows that after four doses of uranium had been given over a period of twenty-one days, the succeeding seven

21 Austin and Eisenbrey Jour Exper Med, 1911, xiv, 366

22 Mosenthal Personal communication

23 Levene and Kristeller Am Jour Physiol, 1909, xiv, 45

24 Green, J. L. Jour Pathol and Bacteriol, 1909, xiii, 296



days showed an average excretion of 129 mg, and the days thereafter 108 mg. The normal, as may be seen in Table 7, was 205 mg

TABLE 6—URIC ACID EXCRETION

Experiment 2	Mg		
Normal average	21		
Nephritis	25	Uranium nitrate,	
	33	8.5 mg subcutaneously	
	123		
	42		
Experiment 3	Mg		Mg
Normal average	14		56
Nephritis	18	Uranium nitrate, 8 mg	49
	27	Uranium nitrate, 7 mg	26
	10	subcutaneously	29
	28		26
	23		29
	23		25
	28		15
Nephritis	44	Uranium nitrate, 7.5 gm	23
	23	subcutaneously	29
	19		22
	26		27
Nephritis	27	Uranium nitrate, 20 mg	31
	18	subcutaneously	19
	58		23
	30		26
	45		20
Nephritis	36	Uranium nitrate, 25 mg subcutaneously	
Experiment 4	Mg		
Normal average	29		
Nephritis	43		
	34	Uranium nitrate, 30 mg	
	56	subcutaneously	
	34		
	17		

*Intravenous Creatinin Injections*—No record of excretion after intravenous injections of creatinin has been found. There are, however, several observations on its excretion when fed or subcutaneously injected. Folin<sup>25</sup> found that if creatinin were ingested by a normal patient, 75 per cent was excreted. Wolf and Shaffer<sup>26</sup> found that 80 per cent of ingested creatinin was excreted. Voegtlin and Towles<sup>27</sup> found that when creatinin was ingested, 36.3 per cent and 62.5 per cent (two experiments) were excreted in twenty-four hours, while if injected subcutaneously, 54.5 per cent and 72.7 per cent (two experiments) were excreted.<sup>28</sup> Mellanby,<sup>29</sup> Lefmann,<sup>4</sup> and Klercker<sup>3</sup> state that ingested

25 Folin, O. *Am Jour Physiol*, 1905, *xiii*, 66

26 Wolf and Shaffer. *Jour Biol Chem*, 1908, *iv*, 439

27 Voegtlin and Towles. *Jour Biol Chem*, 1912, *x*, 479

28 Calculated from protocols

29 Mellanby, E. *Jour Physiol*, 1907-08, *xxxv*, 447

30 v. Hoogenhuyze and Verploegh. *Ztschr f physiol Chem*, 1905, *xlvi*, 415

creatinin is excreted in great part. Van Hoogenhuyze and Verploegh<sup>30</sup> state that 100 per cent of injected creatinin is excreted. The data in Table 8 lead us to the conclusion that when intravenously injected, creatinin is excreted "in toto." From the protocols it will be seen that this did not take more than forty hours.

TABLE 7—CREATININ EXCRETION IN ACUTE URANIUM NEPHRITIS

Experiment	1	2	3	4
	Mg	Mg	Mg	Mg
Normal average	210	190	205	258
Uranium nitrate nephritis	281*	187*	169*	172*
	228	187	174	302
	114	65	74	280
		123	92	170
				90

\* Uranium nitrate subcutaneously. Exp 1, 10 mg, Exp 2, 85 mg, Exp 3, 15 mg, Exp 4, 30 mg.

G *Creatinin Injections During Uranium Nephritis*—No record of creatinin injections in dogs or other animals having uranium or other experimental nephritides has been found. In view of the results, this phase of the subject deserves careful consideration.

TABLE 8—EXCRETION OF CREATININ

Experiment	1	1	1	1	3	3
	Mg	Mg	Mg	Mg	Mg	Mg
Normal (average)	210	210	210	210	165*	127*
Average 3-day period following injection	330	245	223	267	193	141
Average 3-day period with injected amount subtracted	280	209	190	234	163	114

\* Excreted during chronic nephritis.

When a dog with uranium nephritis was injected with an amount of creatinin equivalent approximately to one-half the normal excretion, the animal either died (two cases) or showed a remarkable decrease in renal activity (one case). The data show (Tables 9 and 10) that not only was the injected creatinin not excreted, but the excretion lay far below either the normal or the amount excreted in the previous nephritic period.

TABLE 9—CREATININ EXCRETION AFTER INJECTION OF APPROXIMATELY ONE-HALF THE USUAL EXCRETION DURING NEPHRITIS

	Experiment 2		
	Volume, c c	Creatinin, Mg	Uric Acid, Mg
Average normal	425	190	21
Average after nephritis	615	140	55
Average after creatinin injection	96	65	13

The excretion of the other substances subjected to study shows a noteworthy state of affairs, namely, a great decrease in the excretion of water, chlorids and uric acid, in other words, there was an apparent

arrest of renal function, followed in two instances by death and in one by recovery. This last case (Table 11) deserves further attention, since an examination of the figures shows that after a certain period (three days) the kidney began to excrete more readily, and that the substances increased daily in amount until the creatinin had reached the normal amount, and until uric acid, chlorids and water had far exceeded it, in other words, what appeared to be a physiological compensation took place.

TABLE 10—CREATININ EXCRETION AFTER INJECTION OF APPROXIMATELY ONE HALF THE USUAL EXCRETION DURING NEPHRITIS

	Experiment 1—	
	Creatinin, Mg	Volume, c c
Average normal	210	266
Average nephritis	207	477
Average creatinin injection	3	127

The following is a description of the animals' condition after creatinin was injected. Dogs 1 and 3 will be described together, as they showed practically the same symptoms and in the same order. These dogs one day after the creatinin injection became apathetic. They did not jump about their cages when approached as had previously been the case. Two days later a fine muscular tremor was noted. The dogs lay quietly in their cages. If placed on their feet they were easily bowled over by a

TABLE 11—APPARENT PHYSIOLOGICAL COMPENSATION IN CREATININ EXCRETION AFTER INJECTION OF EXCESS DURING NEPHRITIS

Experiment 4

	Volume, Cc	Creatinin, Mg	Uric Acid, Mg	Chlorids, Gm
Average (normal)	431	258	29	1 513
Average (nephritis)	403	231	41	1 065
Creatinin injection	400	83	36	0 960
	160	50	9	0 736
	70	11	17	0 196
	212	36	14	0 805
	315	94	19	0 882
	545	117	34	1 417
	850	161	37	1 700
	840	184	44	2 688
	270	202		

gentle push and did not jump up again. The following day a coarse tremor was noted which was spasmodic only. The respiration was labored, perhaps due in part to a nasal infection of a purulent nature.<sup>31</sup> The eyes also now showed a purulent discharge. Neither of these inflam-

31 The fact that this infection occurred but one day before death, and after the renal reaction to the creatinin injection had commenced, warrants the belief that it was in no way responsible for the animal's death, and was only a manifestation of lowered resistance due to the toxic influence on the animal as shown by his changed actions and urinary excretions.

matory changes had been present before. In Dog 3, percussion near the scapular spine gave a very active reflex contraction of the fore leg, which on two occasions developed into a clonus. The dogs became more and more apathetic, lying quietly in their cages, not reacting to calls and unable to stand when placed on their feet. This lasted until they died. If at any time after the creatinin injection water was placed in the cages the dogs drank, but vomited at once. Dog 4 showed no symptoms whatsoever and throughout the experiment appeared normal.

But before offering any explanation of these phenomena, the results of creatinin injections in a subacute uranium nephritis must be noted. Here, as the figures in Table 12 show, the secretion of neither creatinin, uric acid, chlorids nor water was affected. It is on this finding that a possible explanation of the phenomenon in the acute nephritis may be

TABLE 12—RESULTS OF INJECTION OF CREATININ DURING SUBACUTE URANIUM NEPHRITIS

Experiment 3

	Vol, cc	Creat- inin, Mg	Uric Acid, Mg	Chlo- rids, Gm	Remarks
Average normal	360	205	14	0.213	
After four uranium injections during 21 days	435	241	26	1.174*	Injected 91 mg creatinin
	325	187	29	0.910	
	280	153	25	0.840	
	260	128	15	0.806	
	300	156	23	0.750	
	225	136	29	0.562	
	255	96	22	0.612	Injected 70 mg creatinin
	340	122	27	0.544	
	415	182	31	0.830*	
	180	100	19	0.396	
	330	142	23	0.528	
	290	77	26	0.464	
	230	99	20	0.506	

\* Raised chlorid excretion due to saline injection fluid

based. In the acute nephritis, the tubules are all more or less severely injured. If to the normal burden (which, as the figures show, is poorly borne so far as creatinin goes), we add the additional burden of excreting more creatinin, we can readily imagine that the injured cells, now taxed far beyond their powers, would fail to act as well as before, and a more or less complete arrest of renal function would result. In subacute nephritis, cellular regeneration or atrophy takes place, so that the kidney probably contains sufficient normal tubular epithelium to take care of a certain amount of creatinin beyond that presented to the kidney by body metabolism, and thus no ill effects occur. What this amount is, and whether it approaches the normal, has not been demonstrated up to now.

The whole matter seems, moreover, to have another interesting side when we consider that creatinin is increased in fever in general.

(Leathes<sup>32</sup>), and specifically in acute fevers, e g, pneumonia (Wolf and Lambert<sup>33</sup>) and typhoid fever (Shaffer,<sup>34</sup> and Ewing and Wolf<sup>35</sup>), and when we consider that the diphtheria, cholera and colon bacilli, as well as the pneumococcus, cause a tubular nephritis (Aschoff<sup>36</sup>)

The manner of production of a kidney condition which would give rise to uremia in certain febrile diseases might be explained as follows. Taking creatinin as an example of a normal urinary substance excreted by the tubules of the kidney, and reviewing briefly what occurred in Experiments 1, 2, 3, and 4, we may conclude that animals with a tubular nephritis and given a hypercreatininemia, showed an arrest of renal function followed in two instances by death. When the hypercreatininemia was omitted, there was no death from nephritis of similar intensity.<sup>37</sup> In other words, hypercreatininemia taxed the kidney beyond its power of function and the margin of safety or limit of function was overstepped.

Let us now suppose the existence of a febrile condition, in which the excretion of creatinin is raised, the tubules would then be taxed beyond the usual. Add to this a tubular nephritis and we have the reverse of what took place in the experiment, that is, instead of tubular nephritis followed by hypercreatininemia we have hypercreatininemia followed by tubular nephritis, both of which would naturally entail similar results, so far as effects on the tubule are concerned.

As stated above, creatinin is taken only as an example of a urinary substance normally excreted by the kidney tubule. There seems no reason to believe that other normal substances which are increased in fever and excreted by the tubules would not act in a similar way, that is, to overtax an already overfunctioning kidney whose condition had been aggravated by a tubular nephritis.

In brief, it would seem probable that the factors which reduced the total functioning powers of the kidney in the above experiments have been a tubular nephritis followed by a further taxing of the tubules by the presentation of excessive amounts of a substance normally excreted by them and that the same factors, even though reversed in order of occurrence, might act in the same way in human febrile diseases complicated by tubular nephritides.

What may cause the uremia, normal or abnormal substances, is not known. We have only been concerned here with the mechanism of the retention of these substances.

32 Leathes, J. B. *Jour. Physiol.*, 1909, *LXXXI*, 205.

33 Wolf and Lambert. *THE ARCHIVES INT. MED.*, 1910, *I*, 406.

34 Shaffer. *Am. Jour. Physiol.*, 1908, *XXIII*, 1.

35 Ewing and Wolf. *THE ARCHIVES INT. MED.*, 1909, *IV*, 330.

36 Aschoff. *Pathologische Anatomie*, 1911, *II*, 450.

37 This has been shown by many of those quoted above who have worked with uranium.

## CONCLUSIONS

1 In acute uranium nitrate nephritis, (1) creatinin is excreted in decreased amounts, and (2) uric acid is excreted in increased amounts (Experiments 2, 3, 4)

2 In subacute uranium nitrate nephritis, (1) creatinin is excreted in decreased amounts (two weeks), but (2) uric acid and (3) chlorids are excreted in increased amounts (two weeks) (Experiment 3)

3 Creatinin injected in normal dogs is excreted "in toto" (Experiment 1)

4 Creatinin injected in acute uranium nephritis causes (1) endogenous and (2) injected creatinin (Experiments 1, 2, 4), (3) uric acid, (4) chlorids and (5) water, to be excreted in decreased amounts (Experiments 2, 4), (6) death may ensue

5 Creatinin injected in subacute uranium nephritis (Experiment 3) is excreted "in toto," and apparently does not affect the excretion of endogenous creatinin, uric acid, chlorids or water since these are unchanged

I wish to express my thanks to Dr Wm J Gies for the valuable assistance I have received while carrying out this work

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## A CASE OF AURICULAR FIBRILLATION WITH A POST MORTEM EXAMINATION

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### CASE REPORT

*History*—The patient, Miss T G, was 37 years old. Her weight was 55 kilos. She was first admitted to St Francis Hospital, Pittsburgh, Jan 17, 1912, her chief complaint being shortness of breath. Dyspnea had been present during the past four to six weeks, during which period she had also experienced palpitation and precordial pain, occasional night sweats had occurred during the past few months, together with frequent "colds," during the course of which the patient would bring up blood-stained sputum. Her past medical history was as follows. She had chorea during childhood, rheumatic fever in 1908 and again in 1911, measles, diphtheria and small-pox in early life. She was not subject to sore throat. The patient had given birth to three healthy children and had had no miscarriages. She had worked hard. Her habits were good.

*Examination*—The physical findings on the day following admission were, in brief, as follows. The patient was a slender, middle-aged woman lying in bed without any apparent pain or discomfort. Her temperature was 98.4 F, pulse-rate 120 to 130, respiration 22 to 24, systolic blood-pressure 120. She coughed occasionally. There was slight cyanosis, but no jaundice nor edema. Her eyes, mouth and tonsils were negative. The external jugular veins were pulsating. The thyroid gland was not enlarged. The thorax was barrel-shaped and allowed only shallow respiratory excursions, there was a pronounced Harrison's furrow. Expiration was prolonged over the upper lobes of both lungs. Numerous moist râles were heard over the entire posterior aspect of the left lung and in the left lower axillary region. There was pronounced precordial bulging and diffuse heaving synchronous with the heart beat, the point of maximum intensity being in the sixth interspace slightly to the right of the left anterior axillary line. The cardiac impulse was marked and sudden and was preceded by a rough vibratory presystolic thrill. The right cardiac border was 5 cm. to the right of the mid-sternal line, and the left border 12 cm. to the left, at the third interspace. A presystolic rumble terminat-

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\* Submitted for publication March 27, 1913

\* From the Hospital of the Rockefeller Institute for Medical Research New York

ing in a sharp flapping first sound was heard at the apex and was followed by a short puffing murmur, heard over a wide area including the left axilla. The second sound at the pulmonic area was markedly accented and louder than that at the aortic area. The rhythm was regular. The abdomen showed marked epigastric pulsation. The blood, urine and feces showed no abnormalities.

*Treatment*—The patient's condition remained unchanged for five days, during which period the pulse-rate averaged 120, the rhythm being always regular and the heart sounds continuing as noted at the first examination. It is not known whether digitalis had been administered before her admission, but on Jan 22, 1912, the tincture of digitalis was first prescribed in the hospital, the dose being 1 dram a day. After the administration of one-half dram, the patient was awakened by severe palpitation. The resident physician noted at this time that the apex rate had fallen to 80 and that the pulse was grossly irregular in rhythm and in force. The patient was not seen by the physician in

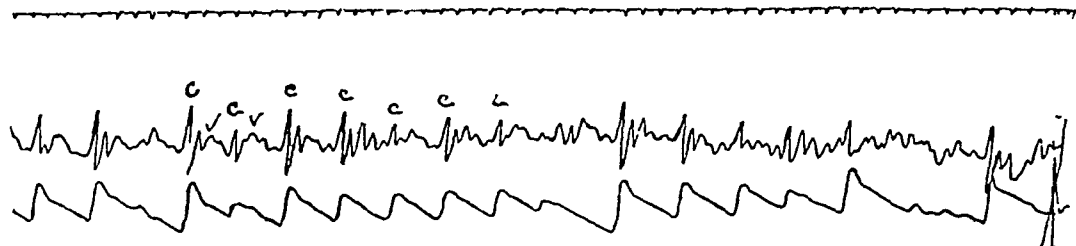


Fig 1—The upper line shows the time in 0.2 seconds. The second and third lines are curves of the jugular (venous) and radial pulses. Complete irregularity of the heart (auricular fibrillation) is present.

charge until 2 drams of the tincture of digitalis had been administered. The medication was then discontinued. It was noted at this time that the presystolic murmur and thrill had disappeared. In a polygraphic tracing taken January 24, the radial curve showed a *pulsus irregularis perpetuus*, and the venous, the ventricular type.

All subsequent tracings were of the same character, so that the conclusion was reached that auricular fibrillation was present. The slower rate of the ventricles continued until the patient was discharged from the hospital, Feb 7, 1912. The change to a slower rate and an irregular rhythm coincided with rapid improvement in the general condition, and also in regard to dyspnea, cough and cyanosis. When the patient left the hospital, the circulation was restored to a condition of compensation.

*Second Admission*—On her second admission, March 12, 1912, the patient was brought to the hospital in a condition of orthopnea. The temperature was 102.6 F, the cardiac rhythm was completely irregular, the apex rate being 110, the respirations were 54 per minute. There was almost constant coughing with expectoration of much thin frothy



fluid which did not contain blood. There was marked general subcutaneous edema. Auscultation of the chest disclosed the presence of numerous fine and coarse râles which could be heard over the entire posterior aspect, resonance was impaired at both bases. The abdomen was dome-shaped and flat on percussion in both flanks. The liver was pulsating and its lower border extended 7 to 8 cm. below the costal margin at the mid-clavicular line. The urine contained albumin and hyaline and granular casts. Next morning at 9.30, after having passed a fairly comfortable night, the patient was in no distress. One hour

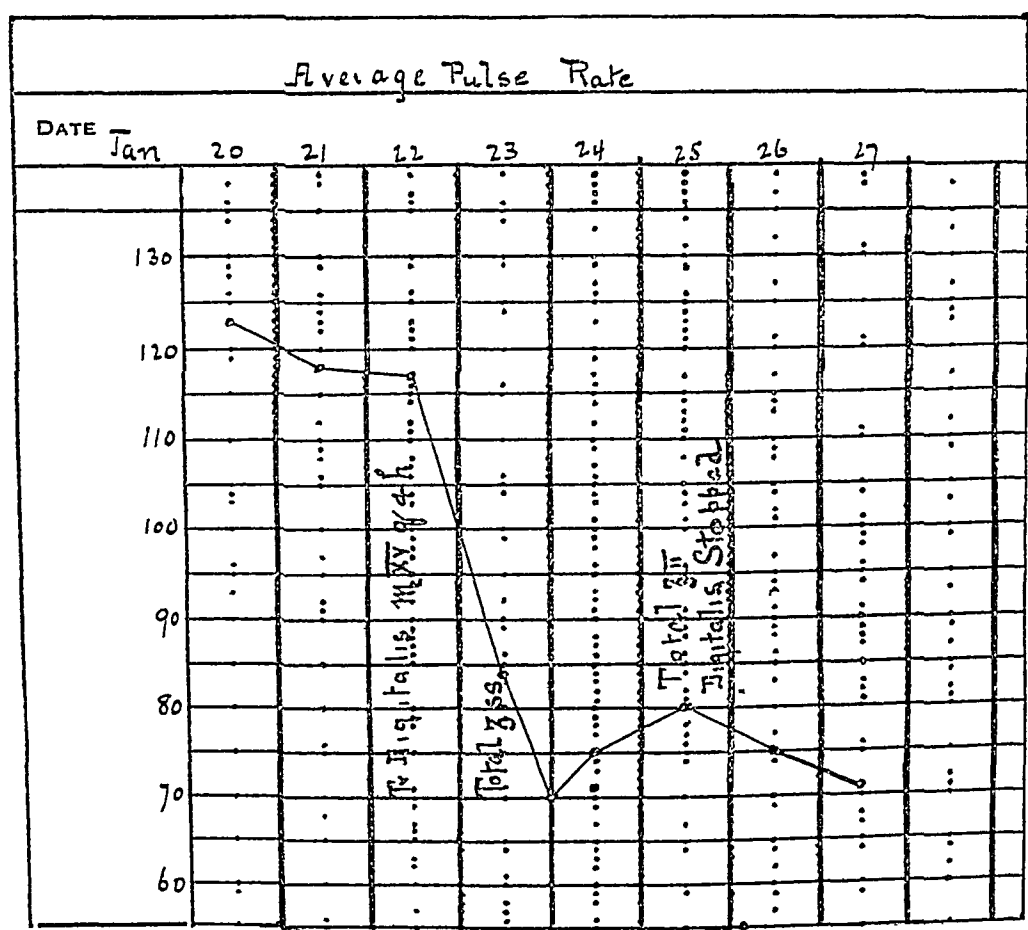


Fig. 2—Chart showing average pulse-rate as affected by digitalis

later she suddenly developed delirium cordis, with urgent dyspnea and general cyanosis. At this time Dr. H. G. Schleiter saw the patient with one of us in consultation, and it was decided to administer strophanthin intravenously, and to follow this by 1 dram of the tincture of digitalis daily by mouth. The injection was subsequently carried out by Dr. Schleiter, who has kindly furnished the following note and the accompanying tracing:

"March 13, 1912. At 11.20 a.m., the patient was in extreme distress, sitting up against pillows and panting for breath. The following con-

ditions were noted. The lower extremities were extensively edematous. The right border of the heart was 2 inches to the right of the mid-line, the left border was 4 inches to the left in the third interspace, the apex, 5 inches to the left in the sixth interspace. The pulse-rate, taken at the apex, was 164 per minute and showed complete arrhythmia. Jugular tracings were not obtainable, but the radial pulse showed beats varying constantly in time and force, with no underlying dominant rhythm demonstrable, it does not appear reasonable to doubt that auricular fibrillation was present. Fluid was present at the bases of both pleural cavities. Many crepitant râles were heard. There was ascites, the liver



Fig. 3

Fig 3—A curve of the radial artery before the administration of strophanthin 0.5 mgm, intravenously



Fig. 4.

Fig 4—The same thirty minutes after the intravenous injection

pulsated and the edge was felt at the level of the umbilicus. The patient was given an intravenous injection of 0.5 milligrams strophanthin. Within five minutes she appeared less ill, and in twenty minutes she was breathing quietly as if after a hypodermatic injection of morphin, the pulse, still showing fibrillation, had fallen to a rate of 116 per minute. A second injection of strophanthin (0.5 milligrams) was given at 3.30 p. m. It is of interest to note that after 7 drams of the tincture of digitalis had been administered, the pulse-rate had fallen to 84 per minute and the patient's condition had greatly improved. The heart

outline had not been reduced, the characteristic irregularity was still present, and the liver border still remained at the level of the umbilicus, where it had been on admission to the hospital."

On the day following and for several days subsequent to the injection of strophanthin, considerable pain and swelling were present in the arm which had been chosen for its administration. Urgent subjective symptoms did not return. During the first three days after the beginning of

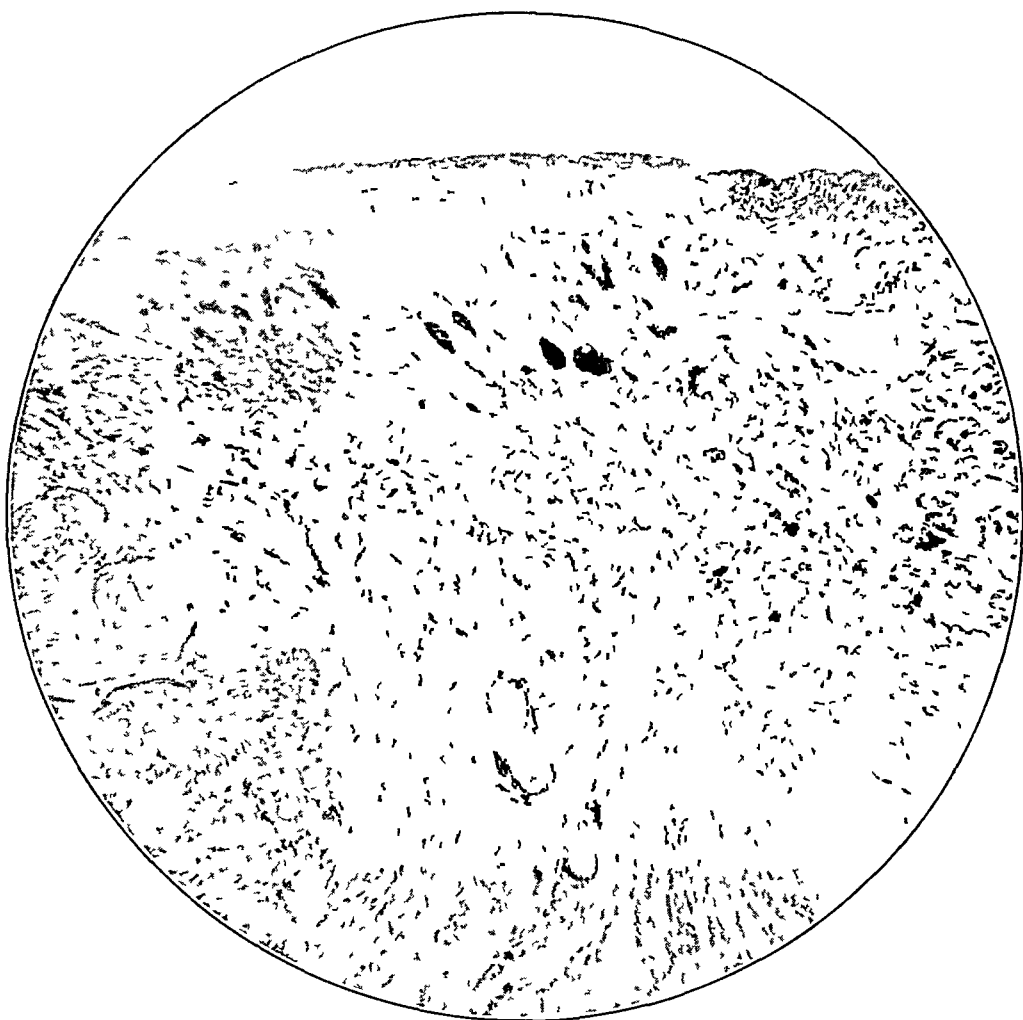


Fig 5—Microphotograph of the sino auricular node. Slide 257. The pericardium is directed upward. The new formed, thin walled blood vessels are seen in the subpericardial fat. The node has a triangular shape, base toward the pericardium.

the administration of digitalis the rate of the heart occasionally reached 120 to 135, but subsequently it fell to normal and remained so after the withdrawal of the drug. Improvement was progressive. On March 24 the urine was free from albumin and casts. The patient was discharged in April, 1912 with the circulation fairly well maintained.

*Third Admission*—About five weeks later, on May 21, 1912, the patient was admitted for a third time. She said that she had been very

comfortable since leaving the hospital, spending most of her time in her chair. She had taken no medicine. The evening before admission she began to be short of breath, the dyspnea soon becoming very urgent. On admission, the patient was found to be in a condition of marked decompensation. She had orthopnea, cyanosis, general edema, anasarca and albuminuria. The temperature was normal, the respirations 40, the rate of the heart at the apex 160, the radial pulse was weak and inter-

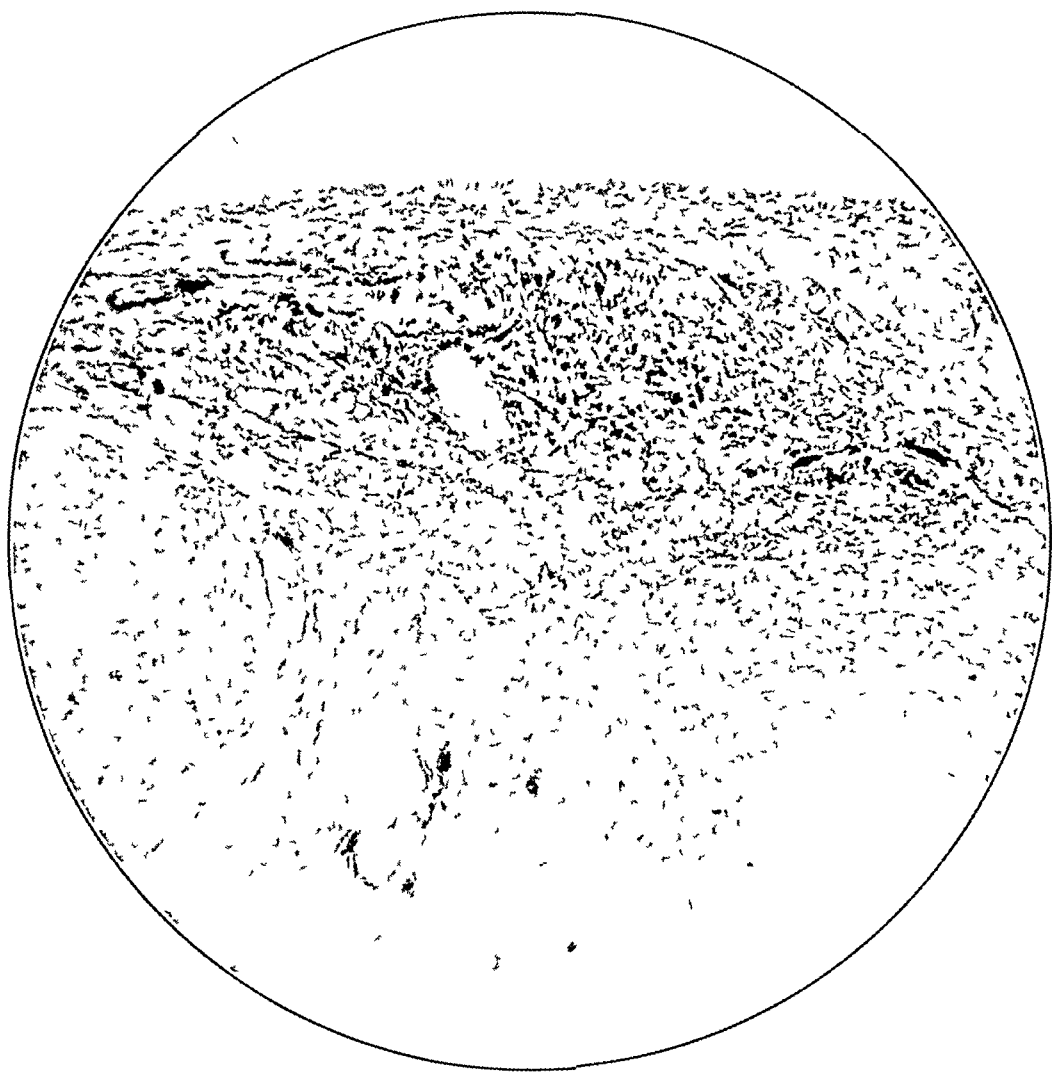


Fig 6—Microphotograph of the sino auricular node. Slide 309. The node has an elongated form, its long axis parallel to the pericardium. A normal relation between muscle and connective tissue is seen.

mittent, the average rate being about 100, the area of cardiac dulness was like that on the previous admission, the lower border of the liver was at the level of the umbilicus. There was constant coughing and expectoration of much white frothy fluid. The patient was given the tincture of digitalis. She had four hours sleep after two injections of one-fourth grain of morphin sulphate. She suffered less discomfort next morning, but in the evening had marked dyspnea, tossed about in bed and refused at

times, to answer questions. Strophanthin (1 milligram) was administered intravenously by the resident physician, but some of the solution escaped into the tissues so that it was not possible to determine the exact quantity which was absorbed. The patient gradually became more comfortable, but no striking change in her condition was noticed. May 23, 1912, the patient was very cyanosed and moved continually in bed. She was stuporous, but responded to questions. Her temperature was normal, the heart rate at the apex was 120, and the radial pulse 80. After a vein had been exposed by dissection, strophanthin (1 milligram) was injected into it, but without apparent result on the heart rate or mass movement of blood. Two days later, May 25, 1912, the temperature suddenly rose to 105.4 F, without a premonitory chill. The patient was very restless. There was marked icterus. The leukocytes numbered 15,000, and in the differential count there were 95.6 per cent polynuclear cells. Twelve ounces of blood were withdrawn by venesection. During May 26, 1912, the temperature again reached 105.4 F. The patient was very restless and cyanotic. On the next day there was progressive failure of the circulation. The cardiac impulse was tapping in character, and the rhythm was grossly irregular. Pulmonary edema set in. The temperature ranged between 101 and 106 F. Death occurred May 28, at 2.30 a. m. Blood-culture showed the presence of an unidentified streptococcus.

An autopsy was performed several hours later by Dr. Oskar Klotz, to whom we are indebted for the report of the post mortem examination.

#### NECROPSY

The body was that of a slightly built woman of about middle age. The nutrition was fair. The pupils were both dilated, the left being larger than the right. The breasts were small and atrophied. There was some excoriation of the skin over the sternum. The external orifices were without change. The skin tissue everywhere showed a marked yellow pigmentation, as did also the sclera.

*Neck Organs.* The trachea was a little congested but did not contain excessive exudate. The lymph nodes at the bifurcation of the trachea showed a single small calcareous nodule the size of a mustard seed. The esophagus showed no change. The thyroid was not enlarged but was rather meaty looking. The tissue of the neck below the thyroid gland appeared edematous, and in it were several dark red lymph nodes.

*Thorax.* There were some old adhesions along the posterior border of each lung. The apex on each side was free. There was no excess fluid in either pleural cavity. The pericardium contained about 75 cc of a clear yellow fluid.

*Left Lung.* The organ crepitated throughout. The tissues appeared a little heavy, but there was no evidence of edema. There was only a slight mottling of black pigment. On section the lung substance was a little congested. The arteries of the lung showed some irregular thickening of their walls. The hilus nodes were not enlarged. The bronchi appeared quite clear.

*Right Lung.* The organ was very similar to that on the left side. There was some slight congestion but no edema. In one of the main pulmonary arteries there was a flat area showing adherent grayish red clot. This clot did not obstruct the artery. The hilus nodes were without change.

*Heart.* See below.

*Aorta* The aorta showed some diffuse thickening of the intima in the arch and in the descending thoracic portion. The carotid arteries showed some irregular nodular areas near the bifurcation.

*Abdomen* On opening the abdomen the partially distended small intestine protruded. The great omentum showed an adhesion to the right of the broad ligament. The spleen was connected by old adhesions to the diaphragm. There were some old bands of fibrous tissue between the left lobe of the liver and the diaphragm. The left ovary had some adhesions to the sigmoid. There was no excess fluid in the peritoneal cavity.

*Alimentary Canal* The stomach and intestines showed nothing unusual. There was some congestion of the lower portion of the small and large intestines. The mesenteric lymph-nodes were not enlarged.

*Liver* The organ was rather swollen and was flabby. The outer surface of the left lobe showed some old adhesions. The organ was quite pale in color. The gall-bladder contained thick brown bile, which contained many pigmented granules. The liver on section was bright yellow, in which some dark red spots and streaks could be distinguished. The lobules were not distinctly marked. There was no evidence of fibrosis. The yellow areas were not definitely depressed but some resembled areas of necrosis.

*Spleen* The spleen was tense and firm. On section the organ appeared dark and firm in certain areas, while in others the tissue was soft and could be readily scraped with a knife. The softer areas appeared more particularly in the center of the organ. The Malpighian bodies were indistinct.

*Kidneys* Both organs were very much alike. In each instance the capsule was quite thin and not adherent. The cortex was gray and somewhat swollen, it was poorly defined from the medulla. The pelvis and ureters were normal.

*Adrenals* Both adrenals were quite large. The cortex was red and showed no evidence of fat. The medulla was not enlarged and was of a gray color.

*Bladder* The organ was of good size. The walls were thin and pale.

*Genitalia* The tubes were both normal. The ovary in the left side contained a cyst 2.5 cm. in length. The uterus was normal in size and appearance. The cervix showed the presence of two old tears. In the vagina there was some excoriation of the epithelium on the posterior wall just below the cervix.

#### MICROSCOPICAL REPORT

*Lymph-Nodes* The lymph sinuses throughout were much dilated, as were also the blood vessels. The sinuses were filled with lymphocytes, a few polymorphonuclear leukocytes and occasional endothelial cells. There was much carbon pigment.

*Lung* The alveoli were of usual size. Their walls were thin and there was no evidence of any inflammatory exudate into the alveoli.

*Heart* Sections of the heart muscle showed a rather poorly staining tissue in which the muscle fibers did not stain evenly. The muscle fibers appeared rather narrow. The striations of the muscle fibers were indistinct and these were seen in broken fragments in the neighborhood of some of the blood-vessels. About these blood vessels was an excess amount of connective tissue. In other places the capillaries lying between the muscle bundles were distended with blood with occasional extravasation of red blood cells into the surrounding tissue. Here and there a number of polymorphonuclear leukocytes were seen in the interstitial tissue. Portions of the heart muscle cut on the freezing microtome showed an abundance of fat deposited within the muscle cells. This fatty degeneration was irregularly distributed through the tissue, in places it was very marked. Islands of connective tissue were also evident in the vicinity of the blood vessels.

*Thyroid* Sections of the thyroid gland showed tissue with many medium sized alveoli containing colloid material. The alveolar walls were quite thin and the epithelium somewhat flattened.

*Kidney* In the cortex of the organ the glomeruli were of good size and they commonly showed fairly wide capsular spaces. The tubules of the cortex were large, many of them had wide lumina and contained some debris. The cells lining the tubules were of irregular size and stained poorly.

*Liver* The structure of the organ was much altered. The central zones of the lobules were almost entirely destroyed, there being no liver columns in these regions. The sinuses were much dilated and there appeared to be an extravasation of red blood cells into the surrounding tissues. Each lobule showed only a rim of liver cells in the periphery.

*Spleen* The organ was intensely congested so that the normal markings were almost obliterated. The Malpighian bodies were small.

#### BACTERIOLOGICAL REPORT

Blood taken a day before death contained streptococci. The biologic character of this organism was not identified.

*Pathologic and Bacteriologic Diagnosis* (Rheumatism), chronic sclerotic mitral endocarditis, stenosis of mitral valve, chronic interstitial myocarditis, chronic sclerotic aortic endocarditis (slight), dilatation of heart (left ventricle and right auricle), hypertrophy of heart (left ventricle), milk spots of heart, fatty degeneration of heart, acute interstitial myocarditis, hydropericardium, thrombosis of pulmonary artery, sclerosis of pulmonary artery, old bilateral pleural adhesions, obsolete tuberculosis of peribronchial glands, chronic congestion of lung, peritoneal adhesions, chronic perisplenitis, cardiac spleen with acute splenitis, chronic perihepatitis, nutmeg liver, bile sand, central necrosis of liver, hemorrhage into liver, cloudy swelling of kidney, enlarged adrenals, cyst of ovary, chronic perisalpingitis, old laceration of cervix, decubitus ulcer of sacrum and vagina, septicemia (streptococcus).

#### TECHNIC OF EXAMINATION OF HEART

*Heart* The heart was fixed in Zenker's solution. The area containing the sino auricular node was washed and hardened in alcohol. The rest of the heart was taken out of Zenker's solution, washed in running water and then sent for examination in a 1 per cent formaldehyd solution. It was then washed and preserved in alcohol. The length of the heart in the fixed state was 12 cm from the auriculo ventricular groove to the apex on the anterior surface, and 9 cm on the posterior surface. There was a moderate amount of subpericardial fat along the right border of the heart, here there was a milk spot measuring 4 by 2.5 cm. A similar one measuring 1.5 by 1.5 cm was found near the apex on the interior surface of the right ventricle. The cavity of the right auricle was dilated but not hypertrophied. The endocardium was white and somewhat yellowish. A small Chiari net guarded the opening of the coronary sinus. The tricuspid valve admitted three fingers; the borders of the flaps were thickened. The right ventricle was neither dilated nor hypertrophied. The pulmonary valve was normal. The cavity of the left auricle was much dilated. The endocardium was thick and white. There were no vegetations. The mitral valve admitted two fingers. The edges of the flaps were much thickened and were rolled in on the auricular surface. The cavity of the left ventricle was slightly dilated but not hypertrophied. The wall measured 15 mm at the base, 17 mm at the level of the papillary muscles and 8 mm at the apex. The outflow tract of the ventricle was more dilated than the left half of the cavity, and the endocardium lining it was white. The chordae tendineae were shorter and slightly thicker than normal. There were two small false posterior moderator bands. The corpora Arantii of the cusps of the aortic valve were thickened. The cusps themselves were adherent to each other at their points of intersection; otherwise they were normal. The coronary arteries were normal. The heart presented no congenital anomalies.

*Sino Auricular Node* The area at the cavo auricular junction containing the sino auricular node was hardened, embedded cut and stained in the manner

employed and described elsewhere<sup>2</sup>. The sections were cut at a thickness of 12 microns at right angles to the long axis, and every fifth section was mounted. On account of the fixation in Zenker's solution, bichlorid precipitation occurred but was removed successfully by immersing the sections in Lugol's solution for one week before staining. The number of sections cut was 2,235, so that the length of the node after embedding was 26.82 mm<sup>3</sup>. The relation of the upper extremity of the node to the cavo-auricular junction could not be ascertained because the tissues had been excised from the heart before it was sent for examination, and the normal morphologic landmarks were consequently destroyed. The shape and dimensions of the transverse section of the node varied at different levels. In its upper extremity it was circular and its diameter was 1 mm. It lay directly under the pericardium, the wall of the auricle measuring 3.5 mm. There was a small hemorrhage close to the node. In the subpericardial fatty and connective tissue and also sometimes encroaching on the substance of the node itself, but confined almost wholly to the nodal area, there were many thin-walled blood vessels, probably inflammatory or degenerative in origin. All of these, as well as the other vessels seen in this series, showed very marked congestion. A short distance below its upper extremity, the node lay 2 mm deep from the pericardium and precisely at the junction of the taenia terminalis and the atrium. It measured 4 by 0.5 mm, the long axis being parallel to the pericardium. The shape was roughly triangular, except that the angles were much rounded off. The structure of the node, aside from the abnormalities noted, was normal, both in the total quantity of muscle present and in the relation of this amount to that of connective tissue. An unusual arm projected outward from its left border toward the pericardium, continued parallel with it a short distance and was finally lost in the muscular structure of the auricle. At a level still lower, the node measured 6 by 1 mm and lay only 0.5 mm from the pericardium. The largest proportions the node attained were 6.5 by 1.5 mm, 13.74 mm from the upper extremity. From this point onward, the dimensions of the node became rapidly reduced and the structure terminated in a tail, the larger part of which was formed of connective tissue.

The relation of muscle to nerves and ganglia was unusually close. At all levels there were collections of ganglion cells in the space between the pericardium and the muscle layer. Nerve bundles, both small and relatively large, were found in the same situations and also within the structure of the node itself. About the nerve ganglia and nerve fibers the new-formed, thin-walled blood-vessels, which have been described, were found in rather large numbers. The artery, which is so often found in relation to the node, had at a low level a distinct reduction in the diameter of the lumen due to an endarteritic process. This vessel showed no other point of interest except collections of smooth muscle fibers arranged in bundles and irregularly distributed about the vessel as an external longitudinal layer, similar to that which has been observed to be about the central venous sinuses of the adrenal glands.

*The Conduction System* The block containing this system was excised in the usual manner. It was cut in sections 12 microns thick in a plane at right angles to the long axis of the heart. Every fifth section was mounted. In the inter-auricular septum both muscle tissue and fat showed the presence of many leukocytes and lymphocytes in groups and also lying between the strands of muscle fibers. The auriculo-nodal junction was of sufficient size but was inflamed. The auriculo-ventricular node was of normal size large rather than small, showing the characteristic interlacing of the fibers but poorer in nuclei than is usual. There was a fairly well marked inflammatory process of the nature described and also moderately large collections of inflammatory cells within the substance

2 Heart 1911 n 245

3 The length of the node in another heart weighing 890 gm. already reported (Heard, 1912 n 24) measured 21.55 mm. Koch (*Med Klin*, 1911 No 12) gives the length as about 3 cm. but cites no specific examples.



of the node. A similar inflammatory lesion was also found near the beginning of the main stem. It lay just outside the bundle and extended a short distance along the sheath. It did not compress the bundle. The main stem was large, well developed, normal in appearance and intact from auricles to ventricles. Just before the division of the main stem into the ventricular branches, there was another area showing an infiltration with leukocytes and lymphocytes. From the point of division onward, the branches, more especially the right, showed only slight inflammatory lesions. Both branches were normal in size, the right a little larger than the left at the beginning.

*Résumé.* The sino auricular node showed normal relations between the amounts of connective tissue and muscle, there was no sclerosis, but an inflammatory lesion in slight part within the substance, but for the most part without, though in the neighborhood of the node. The auriculoventricular node was inflamed to a far greater extent than the sinus node and contained abscess like bodies. Similar smaller collections were found in the main stem. Congestion was a marked feature of the lesion throughout. There was no break in continuity of the conduction system.

#### DISCUSSION AND SUMMARY

A case is described in which, while the patient was under observation, a sequential rhythm changed to complete irregularity of the cardiac mechanism, due to auricular fibrillation. It is extremely doubtful whether the one-half diachm of digitalis which the patient received could have been responsible for the altered rhythm, even if she had been given the drug before admission to the hospital, five days before. Neither can the fall in ventricular rate from 120 to 80, occurring with the onset of fibrillation, be ascribed to an administration of digitalis extending over only half a day. The fall in rate occurring with the onset of auricular fibrillation is difficult to explain, but it occurs in other conditions of which we have only slight knowledge. The action of strophanthin administered intravenously was studied and showed a strikingly beneficial effect on the circulation and the subjective symptoms of the patient. The post mortem examination showed a lesion of the sino-auricular node, but it cannot be definitely asserted that a relation exists between the lesion described and the clinical irregularity that was studied.

# THE RELATION OF HEART-BLOCK TO LESIONS OF THE AURICULOVENTRICULAR BUNDLE, WITH REPORT OF A CASE

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In view of the present interest in the relation of demonstrable anatomical changes in the auriculoventricular conduction system to the changes in the function of this system, the present case may be found of interest. It will serve as an instance of how extensive the anatomical disturbance of the bundle may be without destruction of its function.

## CASE REPORT

*History*—The patient entered the New York Hospital March 18, 1912, on the service of Dr. L. A. Conner, to whose kindness I am indebted for permission to use the case. He was an Italian laborer, aged 23. Venereal infection was denied, nor was there a history of secondary or tertiary syphilitic manifestations. He had used considerable beer and whisky for the last four or five years. He had never had chorea or any rheumatic manifestations. He had had typhoid fever in late childhood, but otherwise had always been healthy until the present illness.

Three months before admission to the hospital, both knees became painful, swollen and tender, and shortly afterward his wrists, hands, shoulders and ankles were similarly affected. He felt feverish, had considerable headache, and perspired freely. He was very weak and so prostrated that he remained in bed. Soon after the onset of the joint symptoms he began to be troubled by palpitation and moderate shortness of breath, and there was also a slight dry cough. His condition had remained about the same until admission to the hospital.

*Examination*—On admission at 12 m., his rectal temperature was 98.4 F, his pulse 82 per minute, and his respirations 20 per minute. He seemed normal in appearance, but slightly dyspneic. The skin and mucous membranes were both pale and slightly subicteric. The eyelids were slightly edematous, the sclerae faintly subicteric. His radial pulses were equal, regular, full and of good tension. The vessel wall was slightly thickened, the pulse wave seemed to have a slow, strong impact and a slow fall. There was no venous engorgement.

The cardiac impulse was felt diffusely in the fifth and sixth spaces, the maximum impact being in the sixth space, 13 cm. to the left of the mid line. The action was strong and heaving, 84 beats per minute and regular. Cardiac dullness extended to the right of the mid line 3.5 cm. in the fourth space and to the left of the mid line 15 cm. in the sixth space, 12 cm. in the fifth space, 8.5 cm. in the fourth space, 7 cm. in the third space, and 2.5 cm. in the second space. A fine systolic thrill could be felt over the upper part of the sternum and in the vessels of the neck. The first sound at the apex was loud and booming and accompanied by a blowing systolic murmur of moderate intensity, well transmitted to the left. The second sound was followed immediately by a low-pitched rumbling murmur which ran through all of diastole except for a very brief pause before the first sound. These signs were localized over an area about

5 cm in diameter about the apex impulse. Outside of this area loud blowing systolic and diastolic murmurs were heard. At the base was a loud, rough systolic murmur, best heard to the right of the sternum in the second space, transmitted in all directions, and heard in the vessels of the neck. There was also a loud blowing diastolic murmur, heard best to the left of the sternum in the third space, but transmitted all over the precordium.

There was no deformity of the bony thorax. The lungs showed no abnormal signs. The abdomen was soft and not distended but was slightly tender in the region of the epigastrium. Liver dulness extended from the sixth rib to the costal margin in the mid clavicular line. The edge was indistinctly felt 5 cm below the tenth rib and was not tender. The spleen was not made out to be enlarged. The inguinal lymph nodes were slightly enlarged and soft, but elsewhere the nodes were not enlarged. The fingers showed faint capillary pulsation and a moderate degree of clubbing. No pistol shot sound was heard over the femoral artery. Both wrists and ankles, though not swollen or reddened, were slightly painful on movement and tender to pressure. Both knees were moderately swollen, tender and painful but not reddened. They contained some fluid and thickened synovial fringes. The legs below the knees were slightly edematous. The blood showed hemoglobin 64 per cent (Sahli), white blood corpuscles 17,700, polymorphonuclears 84 per cent, mononuclears 13 per cent, eosinophils 2 per cent, basophils 1 per cent. The urine contained a very faint trace of albumen, but no casts.

*Management and Course*—During the next forty eight hours the temperature varied from 99 to 101 F. The pulse, 96 and 90 beats per minute on the day of admission, was 80 during the next day and 72 on the morning of the third day. It was always regular, and the rate remained quite uniform, showing no abrupt variation, only as noted, a gradual slowing.

He was kept continuously in bed. Beginning on the morning of March 19 he was given 30 grains of sodium salicylate and the same amount of sodium bicarbonate every four hours. During the night of March 19 he perspired profusely. On the morning of March 20 his condition was noted to be improved. There was practically no dyspnea and the joints were less painful.

At about 4 p. m. on March 20 the patient complained of feeling very weak and became very pale. He said he had never had such an attack before. The radial pulse was imperceptible, the carotid pulsations and apex beat being 36 to the minute. The cardiac dulness and murmurs were unchanged. There was no venous engorgement. The patient was lying in bed and complained of no dyspnea or faintness but felt a slight precordial discomfort, some pain in the epigastrium and great weakness. At 5:15 he was given 1/50 grain of atropin sulphate by hypodermic, but without appreciable effect on the symptoms or pulse.

From the onset of the attack the patient's condition remained unchanged, the symptoms being few and mild. At 7:15, however, he became very dyspneic and restless and had the appearance of moderately severe shock. The cardiac dulness now extended 4.5 cm to the right and 16 cm to the left in the sixth space though the murmurs were unchanged. All over the lungs were heard very many fine and medium moist rales and he soon began to cough up small amounts of thin bloody fluid containing very little mucus. At 7:30 he was given 1/15 grain of strychnin sulphate by hypodermic and the foot of his bed was raised. He continued dyspneic, coughing up bloody material, though less restless and at 9 p. m. was given 1/4 grain of morphin sulphate and 7 grains of caffeine sodium salicylate by hypodermic. At no time was his radial pulse palpable though the heart continued to beat at the rate of 30 to 32 per minute.

At about 10 p. m. his heart action became irregular the irregularity consisting in the frequent occurrence of coupled beats. He seemed to be much better at this time being no longer restless and having less cough and dyspnea. The rales in his lungs were also less numerous. From 10 p. m. until 1:30 a. m. he continued

to improve, the cough was less frequent and his discomfort less. The carotid pulse was still slow and continued to show coupled beats. From 2 to 5 a m the patient slept. On awakening at 5 a m his brachial pulse was recorded by the nurse as 29 per minute, and his respirations as 24 per minute. He seemed to be in good condition and did not complain of any discomfort. Shortly after this he was seen to sit up in bed and reach out for something beside him. He suddenly cried out and fell back clutching at his precordium and was found to be dead.



Fig 1—Jugular and carotid pulse tracings showing complete heart block, auricles 69.5 per minute, ventricles 31.5 per minute

A polygraphic record of the jugular and carotid pulses, taken at 4:30 p m, shortly after the onset of the attack, showed that complete auriculo-ventricular dissociation was present (Fig 1). The auricular rate was 69.5 per minute, the ventricular rate 31.5 per minute. In Figure 2, taken at 5:45 p m, one-half hour after the administration of the atropin, the dissociation was still complete. The auricular rate had increased to 98.4 per minute and the ventricular rate to 34.4 per minute.

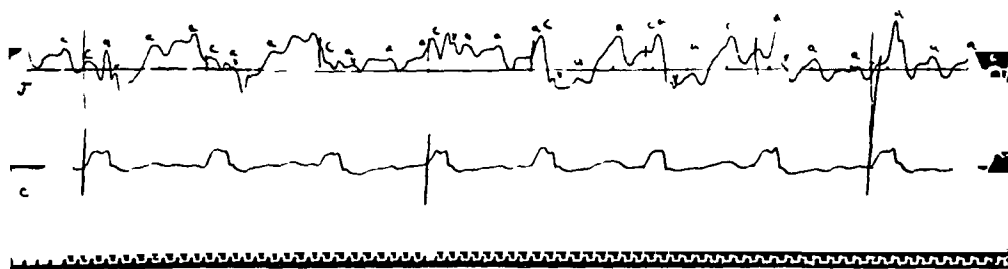


Fig 2—Tracing obtained one half hour after atropin. Complete block still present. Auricles 98.4 per minute, ventricles 34.4 per minute

In a tracing taken two hours after the atropin had been administered, and which it does not seem necessary to reproduce, some of the vagus tone had been regained for the auricles had slowed to 85.9 per minute and the ventricles to 32.1 per minute.<sup>1</sup>

1 It is of interest to note that though the auricular rate showed the most marked result from the paralysis of the vagus endings, still the ventricles seemed also to be affected though to a much less extent.

Figure 3 is a curve taken at 10 30 p m, shortly after the onset of the arrhythmia. No definite auricular waves have been demonstrated in this jugular curve, but it is not felt that this must prove their absence, in view of the distortion of the curve by respiratory waves, and of the fact that even the ventricular waves are not well marked. The carotid curve shows that what would otherwise be a slow regular rhythm of 33.6 per minute is five times irregularly interrupted by beats following the rhythmic beats at intervals of 0.75 second, 0.84 second, 0.60 second, 0.92 second and 0.82 second. In each case the interrupting beat is followed by a pause of the period of the rhythm, i. e., about 1.80 seconds, except in the one instance in which the interrupting beat follows after 0.60 second, and here the succeeding pause is slightly shorter than the rhythm interval. If this coupling were due to the second beat being the result of a stimulus transmitted from a coordinately contracting auricle we should expect to find a wave due to the auricular contraction occurring at approximately the same interval before each of these beats. We should further expect that the time intervals between these interrupting beats would be multiples of some smaller figure representing the auricular rate.

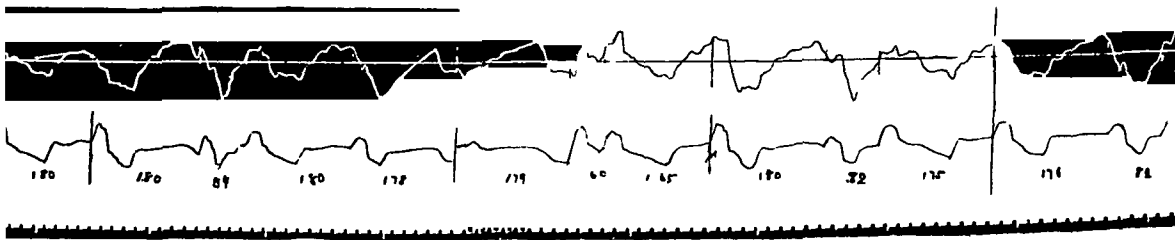


Fig. 3—Tracing obtained after onset of arrhythmia, considered to show interruption of the ventricular rhythm of heart block by ventricular extrasystoles. Figures below carotid curve represent the pulse interval in 0.1 second. The time marks 1/5 second.

As neither of these conditions is fulfilled, it is not believed that the auricle is responsible for their occurrence. The facts could be best explained if complete heart-block were still present and the arrhythmia were due to ventricular extrasystoles.

#### PATHOLOGICAL EXAMINATION

Permission was obtained for only a partial autopsy. The findings, reported by Dr. William J. Elser, were as follows:

"The pericardial sac contained 30 cc of clear serous fluid. The heart is moderately enlarged and all the chambers distended by partially clotted blood. The enlargement is due to dilatation and hypertrophy of the left ventricle. The other chambers are moderately dilated. The myocardium is pale red in color, opaque in appearance and of about normal consistence. There are no distinct focal lesions. The mitral valve is normal in appearance; the mitral orifice does not seem to be enlarged. The aortic valve shows the typical lesions of malignant endocarditis. All the cusps are covered with a large yellowish white

vegetation composed chiefly of fibrin. The substance of the heart has been eroded. The coronary arteries are normal. The arch of the aorta is normal. The pulmonary and tricuspid valves are normal. The lungs appear to be edematous. A blood culture made at autopsy from the left median basilic vein was negative.

"A portion of the aortic vegetation was removed and thoroughly washed in sterile water. It was then crushed and agar plates made from it showed the growth of an organism which proved to be streptococcus locus."

The heart was immediately fixed in formaldehyd Muller's solution, washed and placed in alcohol. After fixation the breadth of the auriculoventricular groove posteriorly was 9.5 cm. The distance from the auriculoventricular groove to the apex was 14 cm anteriorly and 10 cm posteriorly. The thickness of the wall of the left ventricle varied from 1.6 cm to 1.8 cm, that of the right ventricle from 4 cm to 6 cm. The papillary muscles of both sides were well developed that of the left ventricle especially so.

The aortic valves were markedly involved in the process described, as can be seen from figure 4, a photograph of the block excised for microscopical

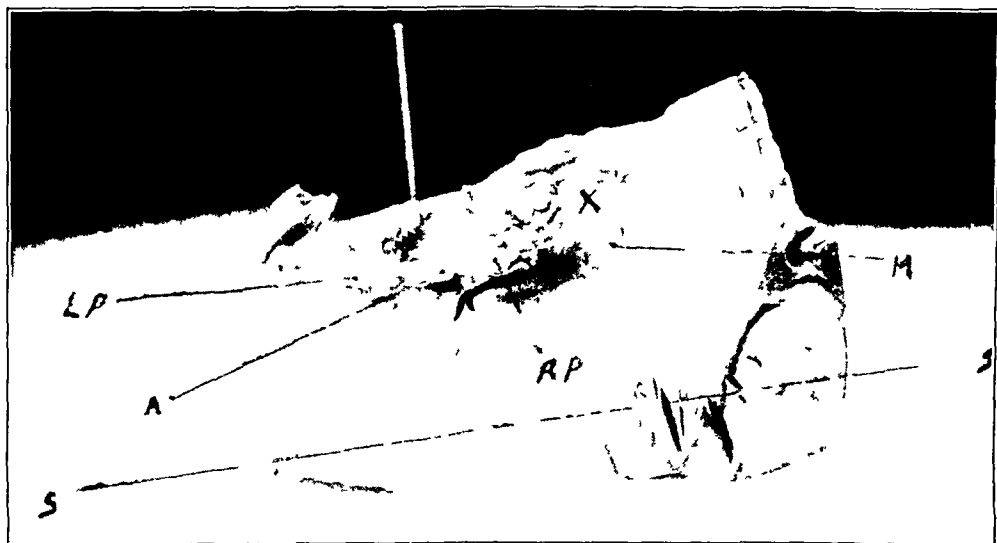


Fig 4—The block removed for section of the auriculoventricular system viewed from the left side. M=cut edge aortic cusp of mitral valve. RP=right posterior cusp of aortic valve. A=anterior cusp of aortic valve. LP=left posterior cusp of aortic valve. X=small aneurysm of the wall of the aorta just above the level of the aortic valve. S—S=plane of section. The course of the node and bundle is indicated by the mark below the right posterior aortic cusp.

examination of the auriculoventricular bundle. The left posterior cusp was least involved; the anterior cusp was most involved. Both the anterior and the right posterior cusps were markedly thickened and the sinuses of Valsalva were almost obliterated. The heart tissue behind and below these cusps was also involved and was markedly calcified as was the tissue filling in the sinuses of Valsalva. The area of calcification below the anterior cusp extended downward in the muscle of the interventricular septum for 10 mm, bulging beneath the endocardium 4 mm at the upper part and 2 mm at the lower. The calcification did not appear to extend below the lower limit of the right posterior cusp.

*Microscopical Examination*—Pieces of tissue were removed for microscopical examination as follows: (1) a portion of the wall of the right auricle so as to include the sinoauricular node; (2) other portions of the wall of the auricles; (3) the portions of the interauricular and interventricular septa which include the auriculoventricular system from the node to well beyond the branching (Fig 4); (4) portions of the outer walls of the ventricles; and (5) portions

of the base of the papillary muscles. The blocks containing the sinoauricular node and the auriculoventricular system were imbedded in celloidin paraffin and cut in serial sections. The other tissues were cut with the freezing microtome.

The walls of the smaller arteries and arterioles throughout the heart did not seem abnormal. The capillaries were everywhere distended with blood and in places small extravasations had occurred into the tissues. The cardiac muscle in the left auricle and especially in the left ventricle and in the interventricular septum showed a diffuse increase in the cells of the interstitial tissue, these being for the most part round cells though there were many endothelial and polymorphonuclear leukocytes. In the left ventricle and especially in the septum, were patches of old myocarditis where the muscle fibers were entirely destroyed. These areas contained many fibroblasts and an increased amount of connective tissue fibrils, but no leukocytes. These areas were especially numerous and extensive at the basal part of the interventricular septum. The muscle of the right auricle and ventricle was more normal showing but a small number of

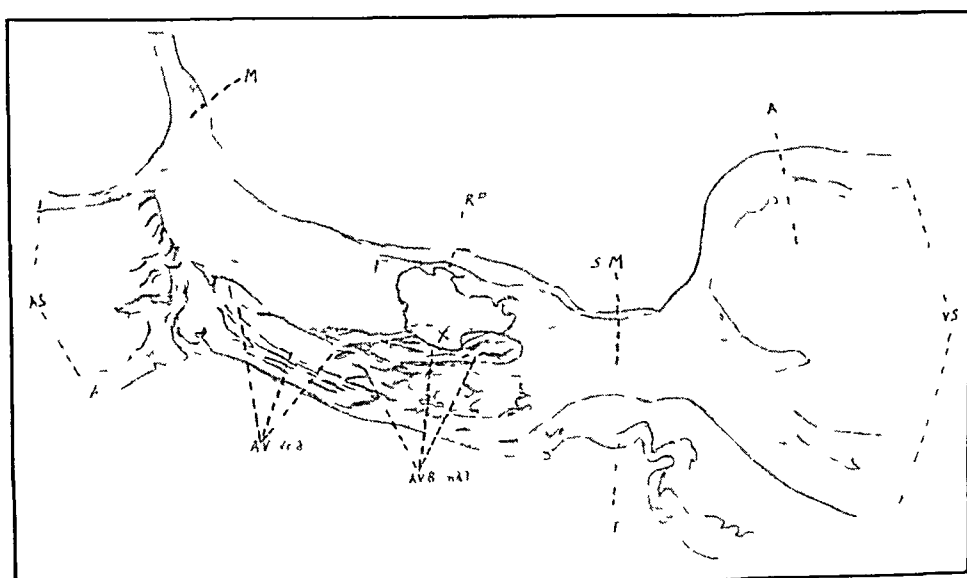


Fig 5—Projection drawing of a section showing at X the probable extent of destruction of bundle tissue. Fibrous tissue is black. Muscle tissue white. Necrotic material shaded. AS=auricular septum. M=mitral valve. RP=necrotic focus below right posterior aortic cusp. SM=septum membranaceum. V=tricuspid valve. A=necrotic focus below anterior aortic cusp. VS=ventricular septum.

round cells in the interstitial tissue and only an occasional leukocyte. The papillary muscles showed a few round cells in the interstitial tissue, and the muscle fibers beneath the endocardium were markedly vacuolized so that the sarcoplasm was at times almost entirely gone from the central part of the fiber, leaving the nucleus supported by strands extending in from the periphery. The nuclei seemed unchanged. The sinoauricular node seemed to be normal, though possibly the fibrous tissue was very slightly increased in amount. The fibers were well striated and there were no leukocytes found here.

Very marked and extensive changes were found in the auriculoventricular system. At 3 mm beyond its origin from the node, the auriculoventricular bundle became involved in the extensive focus which has been described involving the right posterior aortic cusp. This focus extended into the central fibrous body of the heart between the attachment of the anterior cusp of the mitral valve below and posteriorly and the septum membranaceum above and anteriorly, but lying nearer to the former than to the latter. It extended in the fibrous

body from the upper level of the right posterior aortic cusp, downward to the upper level of the interventricular septum lying just beneath (to the right of) the endocardium of the aortic vestibule. The tissue involved was necrotic and in part calcified. For 3.3 mm of its course the bundle passed along the right aspect of this focus—the side away from the endocardium—and became involved in it so that about one half of its thickness was destroyed. The conditions may be better understood by a reference to Figure 5 in which the probable extent of the destroyed tissue is indicated, and to Figure 4, in which the course of the bundle is marked as if seen through the heart tissue. The non calcified areas of this focus were thickly infiltrated with round cells and polymorphonuclear leukocytes and this cellular infiltration extended into the adjacent tissues, into the fibrous tissue of the central fibrous body, into the muscle of the auricular septum above into the muscle of the ventricular septum below and into the auriculoventricular bundle where this crosses through the fibrous body from right to left.

Thus, besides the actual destruction of the tissue of the bundle, which must from the nature of the changes have been of considerable duration, there were indications of a more acute process throughout the bundle and the node. This was probably caused by the streptococcus which was affecting the neighboring valve. There was a diffuse and marked infiltration by polymorphonuclear and endothelial leukocytes with a large number of fibroblasts. This infiltration was most marked opposite to the eroded portion of the bundle and here the polymorphonuclear cells were in excess. Elsewhere mononuclear cells predominated. In the neighborhood of areas of dense connective tissue the fibroblasts seemed to be especially numerous so that the infiltration was very marked along the left aspect of the auriculoventricular node where it lay against the central fibrous body and in the latter course of the bundle and in the right branch, where the fibrous tissue septa were more numerous. The infiltration by leukocytes and round cells extended into the main branches of the bundle, and was well marked as far as these were followed. The node and the portion of the bundle beyond the erosion seemed to be edematous. The communication between the auricle and the node was uninterrupted though involved in the inflammatory process.

#### DISCUSSION

We may consider, then, that when the patient first came under observation, his auriculoventricular conducting system was functioning normally, or at least that impulses were being transmitted regularly from auricle to ventricle.<sup>2</sup>

In accordance with this, his pulse was regular and became slower under the influence of rest in bed quite as was to be expected. He then developed complete auriculoventricular dissociation, which persisted after the vagus was paralyzed by atropin, and continued for thirteen hours until his death. Post mortem examination showed that the auriculoventricular bundle was involved in a chronic destructive process and besides this both node and bundle showed an extensive diffuse acute inflammation.

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2 Though it cannot be denied that the patient may have shown lesser degrees of heart-block i. e. dropped beats or increased conduction time before the period of observation began this is not considered to be probable. In support of this assumption is the fact that he was free from arrhythmia for fifty-two hours before complete dissociation set in—the time when a latent tendency to block would have been most likely to become evident.



The point to be emphasized here is that though the diffuse acute inflammation resulted in complete auriculoventricular dissociation, yet the bundle had been extensively involved in a chronic process—only one-half of its transverse section remaining throughout about 2 mm of its course. Though it had been in this condition for weeks, or more probably for months, yet the patient had never had symptoms which would lead us to believe that it had ceased to function, and moreover he showed no signs of heart-block for fifty-two hours before complete dissociation supervened.

Following the very interesting results which Erlanger obtained by compression of the auriculoventricular bundle, in which the degree of functional disability seemed to be parallel with the degree of trauma, attempts were made to correlate with these results the post mortem findings from clinical material. These attempts have been successful in one particular. No cases of complete destruction of a transverse section of the bundle have been reported in which there was not complete auriculoventricular dissociation. Ten such cases have been found in the literature. Bonniger and Monckeburg<sup>3</sup> report two cases, Heinecke, Muller and Hosslein,<sup>4</sup> Monrad Kiohn,<sup>5</sup> Nagayo,<sup>6</sup> Vaquez and Esmein,<sup>7</sup> Fahr<sup>8</sup> and Cohn and Lewis<sup>9</sup> each report one in which the condition of the bundle was shown by serial sections. Jellineck, Cooper and Ophuls,<sup>10</sup> and Oddo and Sauvan<sup>11</sup> have reported cases in which an extensive infarct and a hemorrhage, respectively, involved the septum in the bundle region and must surely have included it. The cases of Armstrong and Monckeberg<sup>12</sup> and of Cohn and Lewis<sup>13</sup> should be included in this group for a lymphangio-endothelioma in the one case, and an aneurysm in the other, was found in the auricular septum, completely separating the node from the auricular musculature and inducing complete auriculoventricular dissociation.<sup>14</sup>

3 Bonniger and Monckeburg. *Deutsch med Wchnsch*, 1908, No 11, 298

4 Heinecke, Muller and Hosslein. *Deutsch Arch f klin Med*, 1908, *xviii*, 459

5 Kiohn Monrad. *Arch de mal du coeur*, 1911, *iv*, 350

6 Nagayo. *Ztschr f klin Med*, 1909, *lxvii*, 495

7 Vaquez and Esmein. *Bull et mém Soc méd d hôp de Paris*, 1907 Series 3, *xxiv*, 78

8 Fahr. *Virchow's Arch f path Anat*, 1907, *cxlxxviii*, 562

9 Cohn and Lewis. *Heart*, 1912, *iv*, 15

10 Jellineck Cooper and Ophuls. *Brit Med Jour*, 1908, *i*, 796

11 Oddo and Sauvan. *Marseille méd* 1907, *xlv*, 443

12 Armstrong and Monckeberg. *Deutsch Arch f klin Med*, 1911 *cii*, 144

13 Cohn and Lewis. *Heart* 1912, *iv*, 15

14 The case of Cohn and Lewis is mentioned twice here since it showed both complete interruption of continuity of the bundle and complete separation of the node from the auricular muscle.

Opposed to these findings, six cases have been reported in which serial sections have shown that there was no lesion of the conducting system though various degrees of block were present before death. In the cases of Fahr,<sup>8</sup> Krumbhaar,<sup>15</sup> of Price and Mackenzie<sup>16</sup> and of Holst and Krohn,<sup>17</sup> the block was complete. In that of Mollard, Dumas and Rebattu<sup>18</sup> it was partial, while in that of Monrad Krohn<sup>5</sup> the degree was not definitely stated, but was probably complete.

Intermediate degrees of bundle involvement have been found in cases showing both partial and complete heart-block. Some of them have shown very considerable lesions of the bundle with marked destruction of its tissue due to chronic inflammatory processes, and these cases have shown the higher grades of block, usually complete. Where still less marked pathological changes were found, almost minimal at times, complete heart-block has been present in six cases and partial block in four. These are tabulated with their histological changes in detail for more ready comparison.

#### CASES SHOWING COMPLETE HEART-BLOCK

Cohn, Holmes and Lewis. Node is normal except for a few strands of dense hyaline connective tissue and a moderate amount of fatty infiltration. The bundle is invaded by dense strands of connective tissue from the septum membranaceum. There is moderate fatty infiltration of the bundle. Large blood sinuses seriously reduce the diameter of the bundle but there are no signs of an inflammatory origin of these. The connective tissue within the bundle is increased. *Heart*, 1911, 11, 241.

Herxheimer and Kohl. The node shows a slight increase in connective tissue and a few round cells between the fibers. The bundle shows no change, but the fibrous tissue of the septum membranaceum is in part calcified. *Deutsch Arch f klin Med*, 1910, xcvi, 330.

Pibram, Koch and Kahn. The artery to the septum shows hyaline degeneration of its wall and in the neighborhood of this the node is somewhat sclerotic. There is an evident increase in fatty tissue in the node and bundle and there is an area of lymphocytic infiltration in the bundle. The muscle fibers of the node and bundle appear normal. *Berl klin Wchnschr*, 1910, xlvii, 1108.

Flemming and Kennedy. Node and first part of bundle involved in a well-marked inflammation. Show markedly congested capillaries and a few foci of round cells mostly lymphocytes, but a few large mononuclear cells of fixed tissue origin. One large focus in beginning of bundle, mostly lymphocytes, but a few large mononuclear cells and some polymorphonuclear leukocytes, appears to damage the fibers passing through it. There are a number of similar foci in auricle bordering on node. These lesions do not involve a great extent of bundle tissue. *Heart*, 1910, 11, 77.

Beck and Stokes. Bundle beset by numerous hemorrhages and its branches show moderate purulent infiltration. The bundle fibers are separated and surrounded by connective tissue containing many fibroblasts, lymphocytes and a few polymorphonuclear leukocytes. *Jour Am Med Assn*, 1910, lv, 1065.

Hay and Moore. Artery to node and bundle is atheromatous. There are patches of a recent inflammatory process where the bundle perforates the central

15 Krumbhaar. *THE ARCHIVES INT MED*, 1910, v, 583.

16 Price and Mackenzie. *Heart*, 1912, iii, 233.

17 Holst and Krohn. *Quart Jour Med*, 1911, iv, 498.

18 Mollard, Dumas and Rebattu. *Arch d mal du coeur*, 1911, iv, 298.

fibrous body—cells resolving into fibroblasts. This process is patchy in distribution and does not extend throughout the whole bundle. *Lancet*, London, 1906, 11, 1271

#### CASES SHOWING PARTIAL HEART-BLOCK

Gerhardt. The part of the bundle which crosses through fibrous body shows normal muscle fibers, but an extensive cellular infiltration most marked in the immediate neighborhood of the blood vessels. The larger vessels which enter the bundle show a marked thickening of the interior so that the lumen of the larger vessels is markedly narrowed. *Deutsch Arch f klin Med*, 1908, xciii, 485

Griffith and Cohn. Endarteritis of vessels of node and septum diminishing their caliber so that some are entirely occluded. Scattered groups of lymphocytes in interventricular septum about node and to less extent within it. Connective tissue strands separating muscle bundles of main stem. In portions of bundle "granulation tissue with numerous lymphocytes." Diameter of bundle reduced and fibers compressed. *Quart Jour Med*, 1910, 11, 126

Cowan, Kennedy, Paterson and Teacher. Well-marked congestion of node and bundle. Three foci of round cells within bundle, all fairly small, cells mostly lymphocytes, but a few larger new connective tissue cells. Fibers of bundle show degeneration in neighborhood of two larger foci, but are otherwise normal. *Quart Jour Med*, 1911, 14, 35

Butterfield. The node is deeply involved in the morbid process (general acute inflammation of heart substance), particularly in neighborhood of fibrous body where the normal appearances were completely obscured by a dense cellular infiltration of lymphocytes, leukocytes and large mononuclear cells. Throughout the remainder of the node and bundle every vessel was surrounded by an infiltration composed almost entirely of lymphocytes. *Heart*, 1912, 11, 233

It is always necessary, in comparing the histological reports of different observers, to bear in mind the varying importance which may be ascribed to certain findings, in this instance as to whether the amount of fibrous tissue or of fatty tissue exceeds the normal and whether distended capillaries signify anything more than ante mortem or post mortem stasis. The node and bundle lie in proximity to the fibrous ring, which besides forming a sheath about the bundle and its branches, sends dense septa into them, while the node has a loose reticular structure the spaces of which are occupied by connective tissue fibrils. Both node and bundle normally contain a certain number of fat cells, and these are known to vary in amount with age,<sup>19</sup> and presumably vary also with individuals. Referring then to Note 19, it is seen that the pathological changes of those cases showing complete dissociation are not more marked than of those showing but partial dissociation. In fact, all of the cases in the second group of partial block show more marked changes than the first three in the first group of complete block.

The present case, considered before the onset of the acute inflammation, is the only one so far reported in which there was extensive destruction of bundle tissue without evidences of heart-block. The

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<sup>19</sup> Monckeberg. Untersuchungen ueber das atrio ventricular Bündel, Jena, 1908

explanation of this is thought to lie only in the fact that the auriculo-ventricular system is not usually examined unless there are evident signs of heart-block

#### CONCLUSIONS

From a consideration of the above facts it is believed that complete or very extensive destruction of the tissues of the conducting system will result in complete heart-block. Lesser degrees of destruction or varying degrees of involvement of the tissues in other pathological processes, such as fibrosis, lymphocytic, leukocytic or fatty infiltration, may produce (1) complete heart-block, (2) partial block with 2 to 1 or 3 to 1 rhythm or dropped beats, or (3) as in the present case, no block at all. It appears that the cases with the higher degrees of block do not necessarily show marked lesions, and *vice versa*, and that, moreover, complete dissociation may occur with no demonstrable changes in the conducting system.

Clinically, then, the functional capacity does not vary solely with the extent or severity of the anatomical changes in the auriculoventricular node and bundle, a result indeed, which might be expected from a consideration of the pathological physiology of other organs. This statement is not considered as at all contrary to Erlanger's results, for, since these were obtained in healthy animals, the trauma was the only factor affecting the junctional tissues.

As to what the clinical factors are which influence this functional capacity, we know very little. We know, however, from animal experimentation, that certain drugs, as well as asphyxia and increased activity of the vagus nerve, possess the power of depressing it. By analogy it might be supposed that the toxins of pathogenic bacteria or of faulty metabolism, or a deficient blood-supply (local asphyxia?), due to endarteritis or to a failing circulation would also affect it. The case of Price and Mackenzie,<sup>16</sup> in which complete heart-block developed in the course of diphtheria, as well as Krumbhaar's<sup>15</sup> case, which followed typhoid fever, are believed to be instances of the toxic type. Though numerous cases have been reported as occurring in the acute infectious diseases as well as in malaria and diabetes mellitus, still, as they have not been accompanied by autopsy reports to prove the bundle to be intact, we can obtain from them only presumptive evidence of the action of the respective toxic substances. No instance has been found in which endarteritis could be ascribed as the sole cause of heart-block on account of the fibrosis which keeps pace with this process. The observation of Robinson,<sup>20</sup> that some degree of heart-block was present in five of seven cases in which records were taken of the dying heart, is considered an instance of the circulatory type as well as the fact, often noted in the

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20 Robinson Jour Exper Med, 1912, 111, 291

wards, that patients showing partial block when in a poor state of compensation often fail to show this when their condition has improved. It is questionable if vagus activity can be sufficiently increased clinically to be the sole cause of heart-block, though its action in the case of digitalis on a predisposed heart is well known. No conclusive case of this type has so far been reported.

#### SUMMARY

1 A patient with aortic and mitral insufficiency and normal heart action developed complete heart-block and died.

2 Autopsy showed a streptococcus endocarditis superposed on a chronic process of the aortic valve which had involved the substance of the heart.

3 The auriculoventricular bundle had been destroyed for one-half of its transverse section by the chronic process, but this, so far as known, had never produced heart-block.

4 Complete heart-block was produced by an involvement of the auriculoventricular system throughout its whole extent in an acute inflammation.

5 The extent of the lesion of the bundle in the cases which have been previously reported is contrasted with the degree of heart-block which was present at death.

6 It is concluded that the extent of the anatomical changes is not the only factor which induces heart-block.

7 Bacterial and metabolic toxins and deficient local blood-supply are suggested as accessory factors which, in certain circumstances, might act alone.

156 East Sixty first Street

of the so-called hematogenous inflammations of the  
 r grouped as Bright's disease, have been made from five  
 etiological, 2, pathogenetic or histogenetic, 3, functional  
 4, clinical (according to the symptom complex), 5,  
 according to the topography or (b) according to the  
 anatomical changes

correlation of several of these principles have also been  
 y the clinical and anatomical and the etiological and  
 sifications have been closely identified But the diffi-  
 cations which are associated with these imperfect com-  
 pletely led to a desire for simple and uniform methods

l be made in the following lines to present a critical  
 lassifications, the evidence which has been advanced in  
 l to draw attention to some erroneous anatomical and  
 options which have acquired importance in the discussion

Finally, I propose to discuss just how far a classifica-  
 ey lesions seems practically possible

## I

### I THE ETIOLOGICAL CLASSIFICATION

l classification of nephritis has not enjoyed much con-  
 nt on the part of the pathologists It has never been  
 est known works on pathology or medicine In 1905,  
 ei,<sup>1</sup> in his admirable review of Bright's disease before  
 ological Society, revived interest it Muller proposed  
 etiological classification for the present anatomical one  
 at anatomical lesions are not within the possibility of  
 i by the physician The etiological classification, how-  
 d almost directly on the experience and observation at  
 appears therefore better adapted for the needs of the

ssell Sage Institute of Pathology, New York

publication April 4 1913

Morbus Brightii Verhandl d deutsch path Gesellsch,

But Muller was conscious of the difficulty of this undertaking, for he added guardedly that such a classification could plainly be of use only, if the different intoxications and infections always produced characteristic changes in the kidney. In outlining this classification, Muller stated that it was based to a great extent on personal observations, and he was conscious that the chronic types of nephritis could not, on account of their complexity, be included in this scheme.

As was natural, therefore, Muller's recommendations were received with much reserve by both pathologists and clinicians. Indeed, collective experience points to the untenability of this principle, even for the so-called acute inflammations of the kidney.

It is true that in cholera and mercuric bichlorid poisoning the kidney changes are regarded by some as absolutely characteristic, but even if this should be true (and it has not been established beyond all doubt), these are the only two for which such a claim may reasonably be made. We know that the majority of all infections and intoxications does not show specific characteristics.

In a previous communication<sup>2</sup> I enumerated several years ago those infections, which, in my experience, may lead to anatomically similar lesions, these are the general and local streptococcus diseases: angina, pharyngitis, tonsillitis, otitis media and others, further, recent syphilis, the exanthemata and contrary to general belief, pneumonia. Quite recently, Fahr<sup>3</sup> stimulated by Muller's remarks, after a more detailed investigation, arrived at very similar conclusions. It is interesting that he, as well as Kretzschmar,<sup>4</sup> apparently ignorant of my statements, also report the frequent occurrence of severe nephritis in pneumonia. Indeed, the high frequency observed by Kretzschmar has been doubted by others. But this difference of opinion may be explained by the fact that one and the same infectious disease, particularly if epidemic in its appearance, may at different times produce very variable results. In the New York epidemic of pneumonia, which occurred about five years ago with a high death rate, the disease manifested throughout a general septic character. It was associated with purulent pericarditis in an extraordinary degree (almost the rule at autopsy), and generally complicated by severe nephritis. In sporadic cases these are observed much more infrequently. The difference of opinion regarding the character of nephritis in pneumonia is undoubtedly due to the variety of lesions the disease produces under different conditions. Aschoff states that the pneumococcus causes

2 Oertel, H. *The Anatomic Histological Processes of Bright's Disease*. Saunders Co., Phila. and London, 1910, p. 67.

3 Fahr. *Können wir die Nierenkrankheiten nach aetiologischen Gesichtspunkten einteilen?* Virchow's Arch. f. path. Anat., 1912, cex, No. 2 (Literature).

4 Kretzschmar. Cited by Fahr, Note 3.

a tubular nephritis Muller also states that the epithelium only is involved and the glomeruli left free, while others report with equal positiveness the occurrence of interstitial and even hemorrhagic nephritis I have been able to observe, by fortune of a large pneumonia material, the possibility of all these lesions This example illustrates in regard to the pneumococcus and the kidney what has been known in regard to other organisms and organs, namely, that different etiological factors may produce anatomically similar lesions, but that the same etiological factor causes at different times very different lesions

These experiences fully agree with the well-known observations of Asch<sup>5</sup> and others, that the structural and consequently functional changes in the kidney during an infection vary with the presence and location of bacteria and soluble or non-soluble toxins, which in one case may produce necrosis of the epithelium, in another exudation or interstitial leukocytic infiltration, or finally, a hyaline and amyloid degeneration of the vessel walls To these must be added further the virulence of bacterial strains, the reactive ability and peculiarity of the individual and the mechanical conditions imposed by the structural arrangement of the kidney, which are very apt to influence the distribution of bacteria and toxins

Finally, we must consider the importance of mixed infections It is hardly necessary to discuss this well-known point in this connection Everyone is acquainted with the influence which mixed infections exert on the manifestations of even etologically well established diseases

The true pathogenetic significance of the tubercle bacillus is as much under discussion in regard to the kidney as elsewhere Senator held that the nephritis in tuberculosis was a chronic parenchymatous nephritis Fr Muller finds it sufficiently characteristic to separate it from other forms, and treats it as specific nephritis, while recently Fischer and Fahr<sup>3</sup> doubt entirely the existence of a tuberculous nephritis without mixed infection Even if this latter view is deemed too radical it remains certain that in at least many instances it is impossible to separate the effects of the tubercle bacillus from those of the almost always accompanying streptococcus infection Thus it would appear that the etiological classification is open to objection, even in diseases whose etiology has been established Wherever the etiological classification has succeeded in entirely displacing anatomical conceptions it has led to much confusion As example, our ideas of what is meant by diphtheritic or tuberculous inflammations are extremely indefinite, and really more confused than formerly, when simple descriptive terms were in more general

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5 Asch Ueber den Einfluss der bakteriellen Stoffwechselprodukte auf die Niere Strassburg 1904 L Beust



use Etiological terms are insufficient unless qualified by others,<sup>6</sup> clearly then, the etiology alone can in no instance serve as a basis for classification

## II THE PATHOGENETIC AND HISTOGENETIC CLASSIFICATION

The question whether inflammations of the kidney may be classified according to their genesis is both old and new Two subdivisions of this question arise first, is it possible to determine with sufficient accuracy the genesis of every nephritis, and secondly, does an established nephritis retain the features of its development sufficiently to give it a distinct anatomical and functional character This last point is of great consequence to the physician, because he deals almost always with established inflammations For instance, one would be justified to speak of parenchymatous nephritis if a nephritis which commenced with involvement of the parenchyma would retain the parenchymatous alterations to the exclusion or at least indisputable subordination of all other accompanying processes

Virchow,<sup>7</sup> as is well known, combined a definite pathogenetic meaning with his ideas of parenchymatous nephritis A parenchymatous inflammation represented to him a degenerative nutritive disturbance of cells excited by an excess of nutrient material In his opinion, this controlled the whole inflammatory process, parenchymatous degeneration was the expression of inflammation Virchow, therefore, had a perfect right to speak of parenchymatous inflammation, because he believed that the origin and course of the disease rested solely in the parenchymatous changes On the other hand, his contemporary opponents in this matter championed, much like the older pathologists (Vogel's definition inflammation = capillary hyperemia + hydrops fibrinosus), the interstitial vascular genesis and character of the inflammatory process But they, like Traube for instance, employed their idea of inflammation in a manner similar to Virchow For, while Traube differentiated between a circumcapsular and intertubular nephritis, he neglected and even denied any parenchymatous involvement As early as 1860, Traube<sup>8</sup> declared with considerable pride that he had been the first to deny the existence of parenchymatous nephritis In other words, the adherents of the genetic classification were divided, one might say, from the very start, and it may be added, from their standpoints justly so, because their ideas of the fundamental character of inflammation differed These

6 See my discussion on *cynanche contagiosa* in the New York City Hospital Medical and Surgical Report I, 1909, p 213 and ff

7 Virchow Ueber parenchymatöse Entzündung Virchow's Arch f path Anat, 1852, iv, 261

8 Traube Ueber den Zusammenhang von Herz und Nierenkrankheiten, etc, in Gesammelte Beiträge, ii, 970

differences have become only more accentuated since. Indeed, Virchow was consequent enough and never regarded any interstitial process in nephritis as an inflammatory phenomenon, but as a process of repair. It will, therefore, be seen that the ideas of Aschoff in this regard are very similar to what Virchow held in 1852.

These views have never been reconciled by later investigators, although many attempts have been made from Rosenstein's<sup>9</sup> time to the present. Both ideas, Virchow's and Traube's, contained much truth, but not all the truth, and, as is not infrequent under such conditions, both were accepted and continued on authority of tradition unfortunately as *types* of inflammation instead of *evidences* of the inflammatory process. Thus originated and continued the contrast of parenchymatous and interstitial inflammations. Indeed, the most recent ideas of inflammation are as diametrically opposed as they ever were, while some still continue to speak of parenchymatous inflammation, although in a somewhat different sense from Virchow's, others have adopted a teleological conception, they regard, again, much like the older writers, only the reactive exudative changes as inflammatory and exclude all degenerative and proliferative changes entirely. This is opposed by a third group of pathologists, who hold that only the combination of, and intimate correlation of alterative, exudative and proliferative changes constitute inflammation. This group eliminates the conception of parenchymatous inflammation entirely and separates all nutritive and alterative changes from the inflammatory conception unless combined with exudative and proliferative changes. A last group of pathologists regards the inflammatory conception in a still broader and less restricted sense, purely objectively as the sum total of genetically closely related and allied processes which are the results of certain irritants and which present passive and reactive features in varying combinations. This is not the place to enter into the details or the merits of these opinions. They are mentioned here to demonstrate that not only in regard to the genesis of nephritis, but to the very nature of inflammation there exist wide differences of opinion which defeat any attempt at a genetic classification. On one point, however, pathologists agree to-day—that any established nephritis (possibly with the exception of the so-called interstitial nephritis) is a diffuse affection of all kidney structures, but in an uneven degree. Thus whatever views were held of the genesis of nephritis, the terms parenchymatous and interstitial acquired gradually a purely descriptive or topographical significance. This is best illustrated by Orth's<sup>10</sup> position. He states:

I hold it justifiable to speak of various forms of kidney inflammation, because the different constituents of the kidney are concerned in a most unequal

<sup>9</sup> Rosenstein. Die Pathologie und Therapie der Nierenkrankheiten. 1863 and 1894.

<sup>10</sup> Orth. Lehrbuch der speciellen pathologischen Anatomie. 1893, II. 47.

manner. Following, therefore, the principle "*a potiori fit denominatio*," I go so far as to acknowledge a parenchymatous, interstitial and glomerulonephritis. But it must be remembered that no sharp line of demarcation between them is possible, and that their combinations are frequent findings.

Fr. Muller, finally, makes the remarkable but true statement, that these terms are used at present not so much to designate an anatomical condition, but rather a clinical picture.

This confusion of uncertain teleological conceptions, anatomical terms and clinical pictures, has necessarily led to hopeless disagreement, and Heubner declares that the majority of cases of chronic nephritis in practice do not fit in the ordinary scheme and are atypical.

It has already been mentioned that Muller endeavored to introduce the etiological principle with the purpose of preventing further confusion, which is very apt to continue by the use of old or altered terms. But it has been seen that this latter offers no more hope for a useful classification than does the genetic one.

### III THE FUNCTIONAL OR PHYSIOLOGICAL AND CLINICAL CLASSIFICATIONS AND THE RELATION OF ANATOMICAL TO FUNCTIONAL CHANGES

Functional and clinical classifications of nephritis are strictly speaking not identical, although we shall consider them together for convenience sake. The functional takes into account only the altered kidney actions, while the clinical bases its views on the symptom complex, that is the sum total of all functional disturbances in the whole body which accompany or are resultants of the kidney disease.

It would appear from the start that both these methods of classification are beset with difficulties by reason of our limited knowledge of the normal kidney function and the even greater complexity and uncertainty of pathological functions and relations. Furthermore, the variability and lack of constancy on the part of the clinical symptoms would be an additional handicap to a clinical classification.

Nevertheless, both have acquired considerable importance lately, and an effort has been made to establish a functional differentiation of kidney disease. It must therefore be considered in some detail. In this connection we must first touch on certain erroneous conceptions which have resulted from a rather indiscriminate use of anatomical terms. It has become the custom to speak of vascular and tubular nephritis very much as formerly of parenchymatous and interstitial, in a contrasting sense, and to draw a sharp distinction between glomerulo and tubular nephritis. The most elaborate and ingenious distinction between the two forms the basis of Schlayer's views and those of his co-workers. Now it cannot be sufficiently emphasized that every nephritis, be it the product of poisons, or toxins, or whatever else, involves, if one considers time

and topographical action of mutants, all structures of the kidney. It is correct, however, that these structures are affected in an unequal quantitative and qualitative manner<sup>11</sup>

In corrosive sublimate poisoning, for instance, the parenchyma cells suffer very severely and conspicuously from the beginning, but there exists also capillary hyperemia and edema. They are followed rapidly by cellular exudation and proliferation. Now it is held by some that these changes are primarily not inflammatory, but purely degenerative, and that this kidney lesion is a nephrosis and later an inflammatory nephrosis. In order to make this plausible it becomes necessary to disregard the capillary hyperemia in the beginning entirely and to look on the initial edema as non-inflammatory, but of a peculiar specific type (Heineke and Marchand<sup>12</sup>). Does this explanation not seem forced? Do we not come nearer an understanding of the actual occurrence if we regard each of these evidences as an integral part of a unit, namely, what is generally spoken of as inflammatory process? We may, if we please, treat the components of this process separately for the sake of study, but is it a gain to regard them as entities? They do not present themselves as independent processes, but occur in definite genetic progression and relation. Modifications in their appearance are due to time and topographical conditions rather than to deep-seated changes in character. It is, therefore, a mistake to assume that in what is described as glomerulo or tubular nephritis, or in a nephrosis only parts of the kidney suffer and others may escape. Nor can it be claimed that it adds to clearness to know that a patient suffers primarily from a pure nephrosis and shortly afterwards from an inflammatory nephrosis<sup>13</sup>.

But it may further be urged that there exist many kidney injuries due to toxins, etc., in which one of the important parts of the kidney—vascular or tubular—is relatively uninvolved. That is true, but it would be another error to conclude that relatively slight morphological changes are equal to negligible functional disturbances or that apparently well-defined morphological alterations are always equal to great functional disturbances. Pearce, who of the experimentalists is perhaps the most careful one not to lose touch with the morphological side of the question, showed with Eisenbrey<sup>14</sup> that nephrotoxic and hemolytic immune sera cause changes, which, by physiological methods present no evidences of vascular injury, but which are anatomically characterized by exudative

11 A fuller discussion of this much disputed question may be found in my monograph *The Anatomic Histological Processes of Bright's Disease*. Saunders Co. 1910, pp. 45 to 47 and pp. 63 to 67.

12 Heineke. *Die Veränderungen der menschlichen Nieren nach Sublimatvergiftung*. Ziegler's Beitr., xlv. 1903, Marchand's remarks, *ibidem*, p. 241.

13 The definition of "nephrosis" is necessarily as uncertain as that of "nephritis," for the views on the nature of the latter determine those of the former.

14 Pearce and Eisenbrey. *Jour. Exper. Med.* 1911, xiv. p. 306.

glomerular lesions of moderate severity. Vascular, they say, must, therefore, be used in the broadest sense, and that lesions of the membrane controlling the passage of fluid may occur without alteration of the power of the vessel to contract and dilate. They differentiate three groups of functional and anatomical changes: 1. In which little or no anatomical evidence of vascular injury is found, but in which physiological methods show profound vascular changes (arsenic). 2. In which anatomical evidence of vascular (exudative) injury is prominent, but in which physiological tests are negative (hemolytic serum). 3. In which both are prominent (diphtheritic toxin).

These experimental investigations agree with similar clinical and anatomical evidences in human nephritis and demonstrate that the *quality* of morphological changes is of great importance in the relation of anatomical to functional changes. Aschoff has laid much emphasis on this point as we shall see later. It has been a general practice to employ solely a not too exact quantitative measure in the determination of structural changes and certainly an insufficient amount of attention has been devoted to their qualitative character. It may be argued that after a structure has been destroyed, it matters little how it happened. But in the first place important functional changes appear during early and slight changes in a structure, and secondly, destruction is very uneven, very rarely leading to complete annihilation of all cells composing a part. Qualitative structural alterations enter, therefore, into the functional changes throughout an observation.

A last important point, and one to which again an insufficient amount of attention has been paid in the experimental investigations of the kidneys, is the compensatory action of one part for another. We are well acquainted with it in the nervous system, we know a little of it in other organs like the hemopoietic and lymphatic systems and the liver, but in the kidney we are further from understanding it, although observations indicate that it exists in this as in other organs.

These general difficulties of a functional classification are further complicated in particular by the different results and views on the toxic effects of poisons.

The importance of this phase of the subject and the general interest and enthusiasm which has been aroused in it after the brilliant observations of Schlayer, Takayasu, Hedinger and Volhard, demand a somewhat detailed review of their work.

Schlayer and his co-workers<sup>15</sup> base their ideas on a strict division of vascular and parenchymatous injury as revealed by the excretion of

<sup>15</sup> Schlayer and Hedinger. Experimentelle Studien über toxische Nephritis. Deutsche Arch. f. klin. Med., 1907, 1, 90. Schlayer. Untersuchungen über die Funktion kranker menschlicher Nieren. Kongress für innere Medizin, 27. Kongress, 1910, p. 744. Hedinger. Experimentelle Studien über die Wirkungsweise von Nieren und Heilmitteln auf kranke Nieren. Ibid., p. 735.

water, sodium chlorid, potassium iodid and milk-sugar. Their experimental investigations have lately been supplemented by observation on human renal disease. Schlager's experimental work showed that when the tubular cells were destroyed the excretion of NaCl and KI was correspondingly interfered with, while vascular injury led to interference with the excretion of milk-sugar. Urine concentration or water excretion may be influenced in two ways. By tubular injury, which diminishes the amount of solids, or by a hypersensitiveness of the blood-vessels, which increases water secretion tubular or vascular hyposthenuria.

Sodium chlorid is not eliminated in the tubular nephritis, hence the urine concentration is low, on the other hand, sodium chlorid is fully eliminated in the vascular type, therefore concentration is constant and high, for the blood-vessels are hypersensitive.

In human oliguria the milk-sugar excretion is slow, while that of NaCl and KI is normal, it is, therefore, vascular in character. He considers polyuria due to sensitiveness of the blood-vessels. In scarlet fever nephritis the water is increased on account of vascular irritation, while the milk-sugar excretion is decreased, in other words, the vascular activity of the kidney has become disassociated.

The same underlying conditions are found in contracted kidney. It resembles, functionally, the acute vascular nephritis in a disassociation of its vascular activity, i. e., the injury to the blood-vessels manifests itself by an increase of water elimination and diminution of milk-sugar excretion. While, however, the acute nephritis shows both a diffuse anatomical and functional involvement of blood-vessels, the early stages of contracted kidney present, according to Schlager, a diffuse functional injury when the anatomical picture still reveals only patchy disease. These observations and ingenious deductions are very interesting, but it may be justly doubted whether such findings, even if substantiated by further observations, furnish a sufficient basis for classification and warrant utter neglect of anatomical evidence. In the first place important generalizations are drawn from the excretion of a few relatively simple substances under certain artificial and pathological conditions. We must confess, however, that very much is still uncertain of the fundamental laws which govern excretion particularly of more complex compounds. We are quite ignorant of the factors, direct or indirect, which may enter into the rapidity and manner of elimination of one or the other substance. It is only necessary to recall here the contradictory results of experimenters regarding the excretion of water and salt in the study of the normal functions of glomeruli and tubules, and the possibilities of compensatory action. We find further a certain variance in these experimental results with the direct anatomical evidence, and herein rests a possibility of error. The anatomical evidence points strongly to the fact that a strict distinction between vascular and tubular

nephritis does not exist, and that the experimental results may be explained by different reasoning. In disease the conditions may be even more complicated. Erich Meyer's<sup>16</sup> observations have led him to similar conclusions. Aschoff<sup>17</sup> and Suzuki's<sup>18</sup> recent experiments have demonstrated with clearness that the effects of poisons on parenchyma cells show important qualitative differences, some, like uranium and mercuric bichlorid, produce necrosis associated at times with a hyaline dropsical degeneration, others, as in the case of cantharidin, with swelling and vacuolization. More particularly in regard to cantharidin, Aschoff found contrary to the generally accepted view tubular lesions and uninvolve-ment of glomeruli. Aschoff, therefore, concludes that the poisons employed by Schlayer and Hedingel show individual differences and complexity in their topographical action, that cantharidin belongs histologically with greater right to the so-called tubular nephritis and that a division of poisons into vascular and tubular varieties does not seem justifiable. He states: All poisons act primarily on the parenchyma, that is, the different parts of the convoluted tubules, the resulting functional changes are the results partly of the topographical variations in the action of a poison and partly the effects of the poison on blood-pressure. Aschoff's results fully corroborate then the view previously expressed,<sup>19</sup> and emphasizes the necessity of a revision of prevalent ideas regarding the specific actions of poisons. There are other important points in this connection which Aschoff and Suzuki have attacked, notably the significance of vital staining and an attempt to analyze further the structural and functional differences in the tubules. So much remains to be done in this regard that we are far from the possibility of a functional classification of kidney diseases. These considerations do not detract in the least from the value of the experimental observations recorded. They remain important contributions to the secretion of the kidney under abnormal conditions. But one should hesitate, at least at present, to accept these results as a sufficient basis for a classification of kidney inflammations.

But we are even more at a loss in an attempt at clinical classification, which introduces additional difficulties. These have been fully discussed by Fr. Muller, so that it is unnecessary to enter into them again. He pointed out the uncertainty of what is meant by acute and chronic lesions, parenchymatous and interstitial, and the difficulty of the corre-

16 Meyer Erich. Discussion of Schlayer's paper. Kongress für innere Medizin, 27 Kongress, 1910.

17 Aschoff. Zur Morphologie der Nierensekretion unter physiologischen und pathologischen Bedingungen. Verhandl. d. deutsche path. Gesellsch., 1912, VI.

18 Suzuki. Zur Morphologie der Nierensekretion unter normalen und pathologischen Bedingungen. Jena, 1912.

19 See my monograph on Bright's disease, p. 66 B.

lation of the clinical picture and the anatomical lesion. He recommended abolishing the uncertain anatomical nomenclature, and to employ at the bedside only descriptive clinical terms, for instance, instead chronic parenchymatous nephritis, chronic hydropic or anhydropic kidney disease. In view of what has been presented above, Muller's desire to discard old outgrown terms and to substitute a very general directly controllable descriptive terminology is praiseworthy. However, it cannot be regarded satisfactory to employ a purely clinical terminology which at the best is only a repetition of symptoms and gives no idea of the picture of the disease processes underlying them.

Indeed, the desire to correlate clinical symptoms with anatomical pictures is so strong and necessary for the scientific physician that constantly and justly such attempts are being made. The greatest difficulties are encountered, of course, in connection with prolonged kidney diseases, above all the contracted kidney. This finds its reason not only in the complexity of the disease, but in the ever-changing views of pathologists about the origin and nature of that affection. It is, therefore, worth while to present the question of contracted kidney in some detail, as it affords an excellent illustration of the difficulties of an exact classification. The latest most generally accepted views on the pathogenesis and histogenesis of contracted kidney are those of Jores and Prym.

Jores<sup>20</sup> ideas are to some extent a revival of those of Gull and Sutton, namely, that one type of contracted kidney is arteriosclerotic and not inflammatory. Before Jores, Senator and Ziegler had recognized the direct relationship of arterial changes to contracted kidney and had described a type as arteriosclerotic interstitial nephritis and arteriosclerotic atrophy of the kidney. Jores makes the following subdivisions:

- 1 The red granular kidney with uniform fine granulations and of brownish-red color, characterized histologically by interstitial growth with atrophic tubules, which show a more or less regular arrangement. Diseased parts interchange with preserved or even hypertrophied parenchyma. Parenchymatous changes are quite inconspicuous or absent, but arteriosclerosis (?) of the small kidney arteries is very marked.

- 2 The secondary contracted kidney, pale or yellowish pale, characterized histologically by an irregular arrangement of atrophied parts. The still preserved glomeruli present the picture of glomerulo-nephritis. The parenchymatous degeneration is always more or less accentuated, but arteriosclerosis of the smaller arteries is very limited or absent. In this form exists little or no heart hypertrophy, it is marked in Form 1.

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<sup>20</sup> Jores. Ueber Arteriosklerose der Kleinen Organarterien und ihre Beziehung zur Nephritis. *Virchows Arch f path anat* Vol cxxxviii, Ueber die Beziehungen der Schrumpfniere zur Herzhypertrophie. *Deutsche Archiv f Klin Med.* 94.



As a result of his largely clinical observations, Volhard<sup>21</sup> has added a third and combined form consisting of 1 plus a nephritis. In Form 1 he found no functional disturbance, in Form 2 a prolongation of water excretion with no power of concentration, and in 3 the same deficiency plus heart hypertrophy. A fourth type of contracted kidney was occasionally met by him without any rise in blood-pressure and functionally related to the secondary contracted kidney (very rare).

Jores' observations have been supplemented by those of Fahr,<sup>22</sup> Gaskell,<sup>23</sup> and lately by an interesting study of Herxheimer,<sup>24</sup> which agrees in the main points with what I have had occasion to observe in this matter. He found even in the early stages of this disease never an entirely healthy parenchyma, although the vascular changes were much more prominent than those in the parenchyma. Nevertheless, I am of the opinion that these parenchymatous changes must be regarded as of some importance in relation to the character of the disease. They are present at a time when nutritive interference by vascular obstruction is out of question and must therefore be attributed to other irritating influences. The characteristic change in the small vessels should not be confounded with the ordinary arteriosclerotic elastic hyperplasia of larger vessels. It consists of a hyaline swelling of the intima associated with the appearance of fatty substances.

According to Herxheimer, it affects frequently the vasa vasorum of larger arteries, but also the vasa afferentia and loops of the glomeruli, he did not observe this in genuine nephritis. Contrary to the findings of Jores, Herxheimer missed this change in other organs with the exception of the spleen. But the latter is of no significance on account of the frequent occurrence of similar vascular changes under all sorts of conditions. Herxheimer regards the vessel lesions as part of general arteriosclerosis, and believes that toxic agents injure the small kidney vessels, thus leading to hypertonia and contracted kidney. He leaves the genesis of the lesion uncertain, it may be due to a direct poisonous action or possibly an indirect result of alterations in kidney tissue or due to nephrotoxins.

Attention has been drawn to similar vascular changes in other organs, for instance, in the capillaries of the islands of Langerhans in the pancreas. It is considered not unlikely that they form a basis for the development of disease in various organs.

21 Volhard. Ueber die funktionelle Unterscheidung der Schrumpfnieren. Kongress für innere Medizin 27. Kongress, 1910, p. 735.

22 Fahr. Ueber chronische Nephritis und ihre Beziehung zur Arteriosklerose. Virchows Arch. f. path. Anat., Vol. 195, Zur pathologisch-anatomischen Unterscheidung der Schrumpfnieren, etc. Frankfurter Ztschr. f. Path., 18.

23 Gaskell. On the Changes in Glomeruli and Arteries in Inflammatory and Arteriosclerotic Kidneys. Jour. Path. and Bacteriol., 1911, 211, 287.

24 Herxheimer. Verhandl. d. deutschen path. Gesellsch., 1912, p. 211.

Now, while many modern pathologists are inclined to separate the red granular or so-called primary contracted kidney entirely from the groups of nephritis, it may in my opinion still be questioned whether we are fully justified in doing so, or whether the older standpoint, which included it among the interstitial or productive group of nephritis, has not considerable justification. Mention has already been made of the existence of parenchymatous changes, which, although quantitatively slight, show an injury beyond the vascular districts at a time when they cannot be explained by simple quantitative interference with the nutrition of these parts as a result of the vascular involvement. Furthermore, even with due consideration to the different structure in large and small vessel, the different nature of these vascular changes from arteriosclerotic or atherosclerotic lesions and its uncertain relation to the other arteriosclerotic processes, which Herxheimer himself emphasizes, rather point to a direct toxic effect.

Finally, the early focal accumulation of cells in the immediate neighborhood of injured parts closely resembling certain inflammatory reactions, the subsequent irregular formation of granulation tissue and growth of connective tissue, raise the possibility of more diffuse and specific sclerogenic irritating influences.

Conditions in the kidney may in this regard perhaps be compared to certain affections in the liver, notably the cirrheses and subacute liver atrophies. Curiously enough, Jores himself has drawn attention to this in connection with a case of subacute liver atrophy presented to the German Pathological Society. Jores<sup>25</sup> says

"If one goes so far as to regard the destruction of liver tissue as the only essential process and the connective tissue growth only dependent upon this loss, observations which I have made in connection with the case under discussion speak decidedly against such an assumption. For it is noteworthy that in this case of marked destruction of liver parenchyma with a duration of three months, no connective tissue proliferation of consequence has occurred. It demonstrates that besides the loss of parenchyma an additional factor enters into the pathogenesis of liver cirrhosis, this causes the chronic proliferating inflammation or, as S. v. Heukelom expressed it an equally effective degenerative and sclerogenic injury of cells." At the same time Albrecht<sup>26</sup> declared that "if one compared these observations (Jores case) with those of Paltauf, who had seen early connective tissue growth in the liver of phosphorus poisoning, one must arrive at the conclusion that in the first instance existed a toxic action on the liver cells alone, while in the second an irritative action on the connective tissue is added. One must question therefore decidedly whether the connective tissue formation in cirrhosis is only the expression of simple scar formation."

It appears that the conditions in contracted kidney are very similar, and indeed, as shown above, interstitial cell foci and thickening occur before loss of parenchyma would call for cicatrization.

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25 Jores Zur Kenntniss der subakuten Leberatrophie Verhandl. d. deutsche path. Gesellsch. 1907, 11, 320

26 Albrecht In the discussion of Jores article. See note 25

My experience is that the vascular changes do not even generally assume marked dimensions without simultaneous extension of cellular foci and connective tissue thickening, which seems to indicate that all of these changes are correlated rather than dependent (Compare the two excellent illustrations accompanying Herxheimer's article in the *Verhandlungen der Deutschen Pathologischen Gesellschaft*, 1912, especially Figure 2)

It must also be remembered that even extensive arteriosclerosis of small vessels in other organs does not appear to lead to the quantitative and qualitative changes which are characteristic of this form of contracted kidney

These considerations make it probable that the processes leading to the primary or red contracted kidney are evidences of irritative influences within the kidney, of which the vascular changes only form an early and conspicuous feature

It is somewhat doubtful whether the three cases which Gaskell reports as representatives of early and more advanced vascular contracted kidney really belong to this category or not, more properly to the arteriosclerotic kidney as recognized by Senator, Ziegler and others. In Case 34 a specific (syphilitic?) etiology may have been involved. It concerned a young man of 34 years, who died with the diagnosis of dementia praecox (?). On autopsy were found focal brain softening due to extensive and pronounced arterial changes (syphilitic?), extending from the basal arteries throughout the brain. History and other clinical data were unsatisfactory, there were no records of blood-pressure or other diagnostic measures. Moderate heart hypertrophy was present. The kidney appeared macroscopically and microscopically normal, except for thickening and fatty changes of arteries and occasional hyaline glomerules. Parenchyma and interstitial tissue were quite uninvolved. The other two cases are even more doubtful in this respect. Case 38 appears typical of the infarcted kidney of arteriosclerosis (Ziegler), and, furthermore, was complicated by a left-sided hydronephrosis and atrophy due to stone. In Case 39 the kidney is described only as decreased in size and the cortex as diminished, no microscopic examination is given.

Frey has also been unable to uphold entirely Volhard's and Jores' contentions, and Krehl<sup>27</sup> is very sceptical in this regard.

Volhard believes that Jores' secondary contracted kidney (macroscopically yellowish, pale, microscopically with accentuated parenchymatous degeneration and typical inflammatory glomeruli, without, or at least with very limited, arteriosclerosis and no heart hypertrophy) occurs even more frequently than the combined form (Type 3). Frey, how-

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<sup>27</sup> Krehl. See discussion of Schlayer's and Volhard's papers. Kongress für innere Medizin, 27. Kongress, 1910.

ever, has not one case in his series of observations which conforms with all the requirements for Type 2 of Jores. In one case existed a blood-pressure of 195, autopsy showed a kidney macroscopically corresponding to this form, and there was little arteriosclerosis, but, contrary to Jores, marked hypertrophy of the heart. Even Roth,<sup>28</sup> who investigated the relationship of arteriosclerosis to contracted kidney in Jores' laboratory, speaks of contracted kidney without arteriosclerosis as an exception, and of the six cases which he reports, three showed some vascular changes. My records agree with Frey's<sup>29</sup> conclusions in so far as occurrence of diseased renal vessels<sup>30</sup> and heart hypertrophy in contracted kidney are concerned. I must believe that both are the rule and that their absence is irregular and dependent on certain other influences: nutrition, atrophy of muscle, edema, rapidity with which the disease leads to fatal issue, etc. There also seems to be no question that the degree of kidney contraction stands in no direct relation to the degree of heart hypertrophy.

Frey<sup>29</sup> is able to recognize a type of arteriosclerotic kidney already acknowledged by Romberg. This form is characterized clinically by stasis. It was formerly regarded as nephritis and is probably identical with what Bollinger and his school described erroneously as *Stauungschrumpfniere*. A previous communication<sup>31</sup> has discussed that feature of the question fully.

In Frey's opinion the old secondary contracted kidney and Jores' Form 2 are practically identical.

According to these modified views, he differentiates between

1. Vascular contracted kidney (*Nephropathia chronica degenerativa sine circulatoria* of Aschoff), (a) of larger type (Ziegler's arteriosclerotic kidney), (b) of smaller kidney vessels (may include the red granular type of Jores, and the old primary interstitial nephritis of Senator. It is in my opinion doubtful whether this really corresponds to the primary contracted kidney or interstitial nephritis, both of which are more correctly grouped, as explained above, under the productive nephritis).

28 Roth. Ueber Schrumpfniere ohne Arteriosklerose. Virchows Arch. f. path. Anat., clxxx.

29 Frey. Zur Pathologie der chronischen Nephritiden. Deutsche Archiv. f. klin. Med., 1912, cxi.

30 It is questionable whether some of these vascular changes in contracted kidney are not the result of the local inflammatory conditions. A periarteritis may involve the adventitia and perivascular infiltration may combine with fibroblastic proliferation and lead to thickening of the adventitia. This lesion may even extend toward the lumen of the vessel, thereby adding an endarteritis obliterans. A direct toxic action on the intima, particularly in the smaller vessels appears also very possible. The arterial changes in nephritis need reinvestigation. It appears that some of them do not belong to what is generally grouped as arteriosclerosis.

31 Oertel. The Cyanotic Induration of the Kidney. Jour. Med. Research. Boston, June, 1912, xxxi, No. 2.

2 Parenchymatous contracted kidney (*Nephropathia chronica inflammatoria* of Aschoff) including the old secondary contracted kidney and Joies' Form 2

3 The combined form of Volhard nephritis plus arteriosclerosis According to Frey, these types differ correspondingly clinically thus

Form 1, with high blood-pressure and urine stasis (the exact type, a or b, cannot be diagnosticated)

Form 2, with dilute urine, inability of the kidney to concentrate, no heart hypertrophy or high blood-pressure

Form 3, like 2 but plus high blood-pressure and heart hypertrophy

There are, of course, exceptions, the vascular type may show no urine changes, provided the heart action is good, specific gravity and power of concentration may then be normal. Again, the parenchymatous forms do not necessarily show typical functional disturbances

Volhard's views may be summarized in this regard thus

Form 1, normal concentration and water excretion, normal excretion of NaCl and nitrogen

Form 2, hyposthenuria, compensated by polyuria (see Schlayer's explanation above) as long as there exists relative sufficiency of the kidney

Form 3, combination form, probably dependent on a predisposition of Form 1 to acquire nephritis. In Volhard's opinion, it is the old genuine contracted kidney, and has a tendency to uremia

Anatomical as well as clinical subdivisions of contracted kidney are, therefore, still much under discussion, and their character uncertain, particularly whether the old primary or genuinely contracted kidney is only arteriosclerotic in character, or whether it represents, as I am inclined to think, an inflammatory lesion with characteristic involvement of small vessels, or whether, finally, a combination of arteriosclerotic changes superseded by nephritis as Volhard believes

In view of the complexity of the matter and the number of divergent and constantly changing views about the nature of these processes does it appear possible to arrive at any classification at all?

Indeed Krehl's remarks at the Congress for Internal Medicine in Wiesbaden in 1910 were very sceptical

I shall endeavor in the second part of this paper to show just how far a classification appears possible

## II

### CLASSIFICATION

It must be emphasized that all classifications in medicine as well as in other branches of science carry with necessity the weakness inherent to the greater or lesser artificiality of all scientific definitions. Theseus, we are told, erected on the Isthmus of Corinth a column bearing on one

side the inscription, "Here is the Peloponnesus and not Attica," and on the other, "Here is Attica and not the Peloponnesus" But no scientific investigator could safely imitate this mythic hero, for the complexity and variability of all natural phenomena make similar strict divisions based on individual observations and ideas easily vulnerable and perishable The scientific investigator must remain conscious of the fact that his classifications are working tools for the study of phenomena, which in reality lack isolation, but are actual only in their genetic relation and interdependence with others Processes defy strict classification, only the fossilized remnant may be embalmed and laid at rest in a final system

A classification, therefore, in order to be applicable to processes of life, may only cover general characteristics It must confine itself to the substance, the nucleus of the matter, for as soon as it extends to the side lines it merges imperceptibly with others which confuse and defeat the very purpose for which it was designed

Thus an exact classification which, not unlike that of an *actio finium regundorum* in Roman law, attempts to draw sharp boundary lines between it and its neighbors, attempts a separation, which in reality does not exist, and which in practice leads to serious disadvantage and away from truth

Mention should perhaps here be made of a psychological complication in attempts at classification They naturally reflect the view-point of the observer Whatever appears most readily in the classifier's field of vision, or that which he is in the habit of thinking in, is to him the most important principle It colors his whole scheme It is difficult, for instance, for a morphologist to think in other than visual conceptions, his ideas represent definitely related morphological processes, one trained only in physiological methods of research needs much less a dominant morphological substratum for a satisfactory conception

Now if one studies carefully the complicated situation which has been outlined above, one must, I believe, come to the conclusion that it is unsafe, at least at present, to leave entirely the ground of objective morphological experience For etiological, histogenetic, functional and clinical facts at our disposal are, in the first place insufficient, in the second place too variable to serve as basis for a classification of nephritis It appears equally mistaken, however, to introduce subjective views regarding the character of anatomical processes, or to separate more or less arbitrarily certain parts which experience has shown in close union with others Nothing, it appears, is gained by such procedure, it is a source of confusion, leads to academic discussions and does not aid in the understanding of the nature of a disease at all Marchand properly questions what would be gained by speaking of an inflammatory neph-

10sis, instead of an inflammation or of a degenerative or parenchymatous nephrosis? Shortly before his death, Senator expressed to me similar views. Indeed, such individual opinions and ideas regarding the nature of pathological processes change so frequently and there exist so many at one time that one can find, for instance, in a modern text-book of pathology, written by leading pathologists, three different ideas and descriptions of the inflammatory process. And that particular book is for students and practitioners.

Observation shows that "inflammation" is composed of a number of processes, which, on account of their close genetic relation and interdependence and more or less definite course, may be conveniently regarded as a unit. In other words, it is the sum total of processes which appear as the result of certain irritations. But if we go beyond this and assume on the basis of theoretical considerations which can be neither entirely proved nor disproved, that the nature of inflammation is only degenerative, or that it is only reactive for purposes of defense, and that the term inflammation should be restricted to one or the other of these features, then we introduce arbitrary lines of demarkation based on personal opinions and build on these unstable systems. This situation is not improved by the fact that another difficulty arises immediately in determining what is to be included under the passive and what under the reactive phenomena. Some, for instance, regard parenchymatous degeneration as a passive process, others as an active response to an inflammatory stimulus.

Thus the present discussions about the nature of inflammation resemble somewhat the discussions of the old psychologists about the nature of the soul. They gave first a metaphysical definition of the soul, then arranged facts according to it. A greater uniformity of views and a more satisfactory classification in psychology were only reached after psychic phenomena were no more regarded as isolated units or transcendental forces, and after it was appreciated that "soul" is a convenient term for the sum total of our inner experience. Medicine in general still suffers more than other sciences from an effort at medieval definitions. These, however, are for reasons previously given, impossible.

I attempted, therefore, several years ago<sup>32</sup> to rehabilitate a purely descriptive anatomical classification which has the advantage of compatibility with the needs of the clinician and pathologist. It assumes that nephritis designates a unit from beginning to end, and therefore includes all processes which may enter into or may directly modify the expressions of this inflammatory process. It touches in no way on the disputable pathogenesis or the varying topographical involvement, both of which go beyond the possibility of a general classification. It indicates only the predominating pathological feature or features.

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<sup>32</sup> Oertel. Bright's Disease pp. 22-26, 214-215.

The idea of a descriptive anatomical principle for classification is not new. It was successfully, if only partly, followed by Cohnheim, Oltz and others and in this country by Delafield. They used the terms degenerative, exudative, productive or proliferative as useful qualifying adjectives. But following Muller's suggestions and efforts to eliminate antiquated and misleading terms entirely, I propose to go further and make it the underlying foundation for the entire system of classification of the inflammations of the kidney.

Such a classification may be held to be too broad, and therefore insufficient, but it may be properly questioned for reasons previously discussed, whether a scientific classification may offer more than an expression of fundamental or general characteristics.

We obtain thus a classification by groups rather than by individual diseases, and it is my belief that with growing knowledge and necessarily growing differences of opinion in regard to the exact place of diseases, classification by groups will become the best means to serve the more general needs of the physician without interfering with the necessary freedom of thought and opinion of the scientific investigator.

We may, accordingly draw the following sketches:

1. The group of *simple nephritis*, in which occurs cloudy swelling and parenchymatous degeneration, inflammatory edema and serous exudate, associated at times by desquamation and inflammatory proliferation of parenchyma cells. Restitution to integrity.

2. The group of *degenerative and exudative nephritis*, destructive in character, represented by marked and extensive degeneration and necrosis of parenchyma cells, cellular exudate, occasionally, with hemorrhages into glomeruli, periglomerular and intertubular tissue and into tubules. Proliferation of parenchyma cells in glomeruli and tubules, abundant cast formation. The predominating feature may exist either on the degenerative or exudative side.

3. The group of *degenerative and productive nephritis*, destructive and constructive in character, with prominent degenerative, largely fatty changes, much slighter and frequently more localized exudative processes, proliferation of parenchyma cells with the formation of epithelial giant cells, cast formation, appearance of leukocytoid and fibroblastic cells, loss and collapse of glomeruli and tubules, gradual formation of mature fibrous tissue overgrowing wasted and wasting parts, first patchy, then more diffuse. Occasional hemorrhages. Thickening of renal arteries, occasional formation of infarcts.

4. The group of *productive nephritis*, associated with a marked reconstruction of kidney cells and architecture.

a. Diffuse. With less violent but general degeneration and loss of parenchyma and glomeruli by inflammatory obliteration. Marked



regeneration of flat and syncytial-like tubular epithelium with marked distortion of the tubules, and associated abundant irregular overgrowth of connective tissue. Arteriosclerosis of kidney arteries usually prominent, infarct formation occasional (includes in general the old secondary contracted kidney and Jores Form 2, Frey's Form 2, Volhard's Form 2 and probably cases of Form 3. Nephropathia chronica inflammatoria of Aschoff)

b Focal and patchy. Characterized early by a hyaline swelling and fatty degeneration of intima and endothelial cells of the small renal vessels and capillaries, associated with cellular interstitial and periglomerular cell foci and focal parenchymatous degeneration. All of these acquire gradually more momentum, but the involvement of the small vessels remains most conspicuous. It leads to obliteration of their lumen, thereby adding quantitative to the qualitative disturbance. Thus results collapse of affected parts, the extent of which necessarily varies, so that at times the superficial appearance of the kidney may be only very finely granular. The extent of new connective tissue formation is also correspondingly irregular, usually most pronounced around Bowman's capsule. The tubules are relatively well preserved until late in the disease, and epithelial desquamation is insignificant. The disease is usually accompanied by arteriosclerosis of the kidney arteries. (Includes in general, Jores' Type 1, Frey's Type 1, Subdivision b, and Volhard's Type 1, and possibly cases of Type 3. Nephropathia chronica degenerativa sive circulatoria of Aschoff. The old genuine contracted red kidney or primary interstitial nephritis.)

The difference between a and b lies in the fact that in a, a relatively strong or decliningly strong irritative influence has affected the kidney very diffusely, perhaps as the result of a previous severe degenerative and exudative nephritis, in b, a much less severe but persistent irritant, which is never sufficiently strong to produce severe diffuse degeneration and exudation, gradually involves the kidney in disease. It naturally affects the walls of the smaller blood-vessels and the glomeruli prominently first, on account of their exposure by virtue of anatomical structure to irritants and blood-pressure. By almost simultaneous extension of its irritating influence it attacks patches of parenchyma and the neighboring periglomerular parts which respond by focal cell accumulation. Their appearance is then manifest, as we have seen, before any quantitative interference by vascular obliteration is possible. In all forms of contracted kidney heart hypertrophy is the rule.

Finally, one may group as independent non-inflammatory affections the senile atrophy and the true arteriosclerotic atrophy of the Ziegler type. The latter is plainly characterized by patchy loss of substance due to elastic thickening and gradual obliteration of arteries alone. It does

not show an atrophy of glomeruli or tubules due to other reasons, scar formation remains, therefore, quite limited and follows strictly in the path of the lost substance

In a previous communication,<sup>33</sup> it has been shown that a cyanotic induration, *Stauungsschrumpfnere*, does not exist, and that cases thus described are either of Groups b, productive nephritis, or of the arterio-sclerotic non-inflammatory atrophy of the kidney associated with stasis

30 West Forty-Fourth Street

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33 Oertel The Cyanotic Induration of the Kidney Jour Med Research, Boston, 1912 xxv, No 2

# THE ETIOLOGY AND TREATMENT OF HEMOGLOBINURIC FEVER

A REPORT OF FIVE HUNDRED AND FOURTEEN CASES

CARL LOVELACE, M D

WACO, TEXAS

The exact etiology of hemoglobinuric fever is still undetermined. It has been considered the result of pernicious malarial infection in instances in which quinin will give relief,<sup>1</sup> others consider it evidence of quinin intoxication,<sup>2</sup> still others that we have here a duplex disease,<sup>3</sup> quinin in some cases giving relief, in others hastening a fatal termination, a disease *svi generis*,<sup>4</sup> where quinin is neither injurious nor beneficial. Some have advised the use of quinin only when the parasites can be demonstrated in the peripheral blood,<sup>5</sup> still others believe that hemoglobinuric fever can be avoided if the quinin is given intramuscularly.<sup>6</sup>

Considering, then, the conflicting opinions as to the nature and treatment of hemoglobinuric fever, it is hoped that this article, based on 514 cases of blackwater fever, treated by American physicians in the hospital of the Madeira-Mamore Railway Company, Porto Velho, Brazil, between Jan 1, 1908, and Nov 27, 1912, may be of interest.

It is proposed to consider (1) the relation of the disease or condition to malaria, (2) its relation to a particular species of malarial parasite, (3) its relation to quinin, (4) its racial and personal incidence.

Under treatment, it has seemed best to discuss (1) the results of treatment with quinin, (2) the results of treatment without quinin, (3) the general treatment of the condition, and (4) the relation of the quinin prophylaxis of malaria to blackwater fever.

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\* Submitted for publication Feb 14, 1913

1 Brem, Walter V. Malarial Hemoglobinuria. Jour Am Med Assn, 1906, viii, 1896

2 The Quinin Theory of Blackwater Fever, suggested by Vertas, a Greek physician, in 1858, supported by Koch, Plehn, Tomaselli and others. Manson Sir Patrick Tropical Diseases p 238

3 Brem, Walter V. Studies of Malaria in Panama, II. THE ARCHIVES INT MED, 1911, vii, 153

4 Manson's Theory, supported by Craig, C F. Is Hemoglobinuric Fever a Manifestation of Malaria or a Disease *Sui Generis*? THE ARCHIVES INT MED, 1911 vii, 56

5 Bastianelli's rule quoted universally. Manson Tropical Diseases, p 244

6 Castellani and Chalmers. Manual of Tropical Diseases, p 696

## RELATION TO MALARIA

(1) Of 327 cases of blackwater fever treated in this hospital between Jan 1, 1911, and Nov 27, 1912, malarial parasites were found in the peripheral blood in 145, or 44 per cent, either on admission or within a few days thereafter. This becomes more significant when the following circumstances are considered (a) In a majority of the cases only one blood examination was made, and it was made during the period of hemoglobinuria (b) Over a considerable portion of the period of time here considered it was my custom to begin quinin very shortly after the disappearance of the hemoglobinuria, so that subsequent examinations were almost necessarily negative. During the year 1912, when the interim between the termination of the hemoglobinuria and the resumption of quinin was longer (five to seven or more days), blood examinations were made more frequently, with the result that the blood-slides of seventy-nine out of 153 cases of blackwater fever showed malarial parasites, a percentage of 51.5 (c) In the considerable number of cases in which quinin has been deliberately withheld for the purpose of making blood examinations, parasites have appeared within fourteen days in all instances save one. At least ten such experiments were made within the year 1912.

(2) No case of blackwater fever has been observed in which there was not a history of a fever, apparently malarial, a few days or weeks previously. Almost invariably there is the history of many attacks extending over many months.

(3) In no instance has hemoglobinuria been observed as a concomitant of a first attack of malaria.

Sick men, not well men, are the ones who have blackwater fever. Men who have lived here some months, who are anemic, whose spleens are enlarged, who are in the habit of having fever every few days or weeks, who, as a rule, take quinin irregularly and inadequately, who insist on getting up and about their businesses immediately after a malarial paroxysm—these are the men whom one soon learns to classify as “blackwater candidates.”

## BLACKWATER FEVER AND THE TERTIAN PARASITE

J. W. W. Stephens has attempted to account for the absence of blackwater fever in Ceylon by the rarity of the estivo-autumnal parasite there.<sup>9</sup> Deaderick writes that “only exceptionally is hemoglobinuria associated with the benign organisms.”<sup>10</sup> Christophers and Bentley, in explaining the hemolysis, assume that the estivo-autumnal parasite is the primary

<sup>9</sup> Castellani and Chalmers. *Manual of Tropical Diseases*, p. 691.

<sup>10</sup> Deaderick, W. H. *A Practical Study of Malaria*, p. 153, *et seq*.

cause of the condition <sup>11</sup> Brem states that, in Panama, the estivo-autumnal parasite is nearly always the one concerned <sup>12</sup>

There is a general tendency to regard the association of the tertian parasite with blackwater fever as accidental, and to assume that the estivo-autumnal parasite must also be present, although perhaps not demonstrable in the peripheral circulation <sup>13</sup>

It is believed that the accompanying tables present evidence for regarding the tertian parasite as a factor, at least as important as the estivo-autumnal, in the production of blackwater fever Table A is a record of the blood examinations in the Candelaria hospital during the past twenty-sixth months It shows, simply, that the estivo-autumnal

TABLE 1—RECORD OF BLOOD EXAMINATIONS FOR MALARIA IN THE CANDELARIA HOSPITAL, FROM SEPTEMBER TO OCTOBER, 1912, INCLUSIVE

Period	Total Blood Examinations	E A	Tertian	E-A and Quartan Tertian	
Sept to December (inclusive), 1910	2257	831	359		63
Year 1911	8029	3130	1481	6	181
January to October (inclusive), 1912	6148	2027	920	10	147
Totals	16434	5988	2760	16	391

TABLE 2—BLOOD EXAMINATIONS OF BLACKWATER FEVER PATIENTS IN THE CANDELARIA HOSPITAL, 1910, 1911 AND 1912

Period	E-A	Tertian	E-A and Tertian	Negative	No Report
1910—(deaths)	1	1	0	4	5
(discharges)	19	22	1	31	51
1911—(deaths)	3	4	0	8	0
(discharges)	24	23	1	88	2
1912—Jan to Oct, inc (deaths)	3	4	0	12	0
(discharges)	37	20	15	62	—
Totals	87	74	17	205	58

parasite occurs here with more than twice the frequency of the tertian parasite Table B is a record of blood examinations in the blackwater fever patients during the same period It is seen that, while the total occurrence of the estivo-autumnal parasite is twice that of the tertian, its occurrence in patients ill of blackwater fever is only slightly greater than that of the tertian parasite, that is to say, a man in this region who harbors the tertian parasite, has nearly twice the liability to hemoglobinuria of a man who harbors the estivo-autumnal parasite These blood-examinations have been checked, at intervals, over considerable

11 Castellani and Chalmers Manual of Tropical Diseases, p 692

12 Brem, Walter V The Etiology of the Erythrolytic Type of Hemoglobinuric Fever THE ARCHIVES INT MED, 1912, ix, 129

13 Deeks, W E and James, W M Pacific Med Jour 1912, iv 347

periods of time, by Dr J S Foisythe, Dr E J Whitaker and Dr A M Wolcott During the past eighteen months particular attention has been paid to identification of the species of parasite in cases of hemoglobinuria

It is believed that, assuming the malarial origin of the condition, the number of cases is sufficient to justify the assertion that the tertian parasite cannot, in this region, be excluded as an important factor in blackwater fever In this connection it may be well to state that, while the tertian parasite is apparently not concerned in any of our cases of "pernicious malaria," it is here an extremely persistent infection More time and more quinin are required for its eradication than for that of the estivo-autumnal parasite In saying this, I am not unmindful of the fact that I have seen crescents persist in the peripheral circulation after quinin, in full doses (30 to 40 grains), had been given daily for three weeks Every physician here who has correlated his clinical and his laboratory work has been struck by the rapid blood destruction in, the great prostration incident to, and the diabolical persistence of tertian infections I cannot here enter into the proof of these unorthodox statements I set them down because I believe them to be true and because of their bearing on a question which has not had the consideration that it deserves, viz, that of the local variations of malaria One cannot read the treatment of malaria as set forth in many of our text books without being struck by the mildness of the measures considered adequate to cure it

#### BLACKWATER FEVER AND QUININ

The association of quinin in this series of cases of blackwater fever has, I believe, been invariable Always there is the history of quinin in one or more small or large doses having been taken a few hours before the onset of the characteristic symptoms Once these symptoms have occurred, however, they are prone to recur while the patient is still in bed, even without quinin or without any other apparent extrinsic cause At times these recurrences are coincident with the demonstrable sporulation of a group of malarial parasites More frequently the blood is negative In one of Whitaker's cases, there were six such recurrences spread irregularly over three weeks

Recurrences after the patient is up and about — that is, *repeated attacks* — seem, here, to be brought about in the same manner as the first attack, they follow a dose of quinin taken for what appears to be a frank demonstration of malarial infection One of our employees treated successively by the writer, Foisythe, Wolcott, Nutter and Whitaker, had fourteen such attacks in three years In each instance a dose of quinin was followed by one or more paroxysms of hemoglobinuria, which paroxysms were in turn followed by a temporary cessation of the active symptoms of malarial infection

In an intensely malarial region it is of course quite natural that a man should, when he begins to feel ill, forthwith take a dose of quinin. Nevertheless, we do receive a goodly number of simply malarial patients who have not taken quinin, we do not receive any blackwater patients who have not taken quinin shortly before the appearance of the hemoglobinuria. It is by no means an uncommon spectacle to see a malarial subject develop blackwater fever in the hospital after the administration of quinin. For the past three years I have used the hydrochlorid of quinin almost exclusively, except for intra-muscular injections. To see the urine of a malarial patient become hemoglobinous after the administration of quinin hydrochlorid has been, in this hospital, an event too common for more than a passing comment.

#### RACIAL AND PERSONAL INCIDENCE

The well-known relative immunity of the negro and negroid races to blackwater fever is very well shown by our records. Of 26,656 admissions for all causes in the past forty-six months, there were 4,537 West Indian patients. These contributed only five to 493 cases of blackwater fever. Two of these were full-blooded negroes. Among 5,751 Brazilian admissions, there were fifty-two cases of blackwater fever. The white Brazilians and, to a lesser degree, those of mixed white and Indian blood, are the ones in whom the disease occurs. The possession of negro blood seems to confer an almost absolute immunity. The possession of aboriginal Indian blood confers only a certain degree of immunity.

During the same period among 6,121 admissions to our Spanish ward, there were 245 cases of blackwater fever, that is to say, 23 per cent of the total admissions, for all causes, furnished 50 per cent of the blackwater fever patients.

Among 14,759 European and white North American admissions, there were 390 cases of blackwater fever. The Spaniards forming 41 per cent of the white admissions, yielded 60 per cent of the blackwater fever. In other words, the liability of the Spaniard to blackwater fever is, here, twice that of other white men. It is more than 50 per cent greater than that of the Portuguese. It is, of course, absurd to consider the remarkably high incidence of the condition among the Spaniards as due to any special racial susceptibility. The explanation lies in the character and habits of the Spanish laborer. Where another man would be glad to go to the hospital, the Galician peasant, when he is working by contract, will dose himself with quinin and continue to work. He will not sleep under a mosquito net and is, therefore, being constantly reinfected with malaria. He takes a great deal of quinin irregularly. He is, more than any of his fellow laborers, a half-treated subject of chronic malaria.

Our Greek laborers, who take 10 grains of quinin daily with clock-like regularity, are relatively free from malaria and, therefore, from hemo-

globinuria This I think, is not due to any racial immunity, but to their character and habits, that is, their obedience to instructions in the matters of mosquito protection and quinin prophylaxis The liability of the Greek to blackwater fever in his own country is notorious

The transient character of a population of railroad employees in the tropics makes it difficult to present figures which show accurately the manner in which length of residence in this region affects the incidence of blackwater fever In general, people not previously infected with malaria, do not suffer from hemoglobinuric fever until after eight or ten months here Individual history with reference to malarial infection and the treatment thereof appears to determine susceptibility The condition developed in one of my patients ten weeks after his arrival, but he had had a severe attack of malaria two weeks after arriving and recurrent attacks weekly until the onset of the hemoglobinuria

One may say, then, that here the negroes have an almost absolute immunity to blackwater fever, that the people originating from the aboriginal inhabitants have a considerable relative immunity, and that there is a distinct personal immunity among Europeans and white North Americans, conferred by the prophylaxis and proper treatment of malaria

#### THE TREATMENT OF BLACKWATER FEVER

The first question here is the much vexed one of quinin All discussion is futile save that which presents actual figures for comparison

During the year 1908, ten cases of blackwater fever were treated here by the method of giving quinin as in ordinary malaria Of these, three died During the year 1909, sixty-eight cases were treated here, some with and some without quinin Of these, seventeen died Our mortality, up to Dec 31, 1909, was, then, 25.6 per cent At this time I felt that it was justifiable to give quinin to a blackwater fever patient Reports of cases treated in Panama by the quinin method had shortly before been published,<sup>1</sup> and the canons of Bastianelli, pronounced "sensible" by Manson, and quoted, apparently with approval, by Osler, enjoined quinin whenever parasites were found in the patient's blood

Toward the end of the year 1909 it was decided to treat all cases of blackwater fever without quinin, whether or not parasites were present Except in two or three regretted instances this decision has been adhered to Disregarding these, 436 cases have been treated without quinin Of these, fifty-one have died — a mortality of 11.6 per cent

J W W Stephens<sup>14</sup> gives the mortality of blackwater fever at from 10 to 20 per cent Deaderick cites 1,006 patients treated without quinin, with a mortality of 11.1 per cent, 472 patients treated with quinin, with a mortality of 25.9 per cent, and 3,210 patients treated by both methods

<sup>14</sup> Osler's Modern Medicine, 1, p 449



with a mortality of 21.3 per cent. Considering that nearly all of the patients treated in this hospital were drawn from immigrant railroad laborers, who worked under a tropical sun, lived crowded together in hastily improvised huts and tents, and suffered much from the ravages of beriberi and bacillary dysentery, it is believed that a death rate of 11.6 per cent, under a non-quinin régime, is sufficient reason for questioning the soundness of Bastianelli's oft-quoted rule that quinin should be given to a patient with hemoglobinuria if parasites are present in the peripheral circulation.

But it is not only empirically that this rule is unsound, it is an indisputable fact, as shown by Stephens, that malarial parasites are practically always present in the peripheral blood of blackwater patients in the beginning of, or just before, the attack, and that they disappear from, or become scarce in the peripheral blood very soon after the urine becomes hemoglobinous. Indeed, a paroxysm of hemoglobinuria in a malarial patient may be compared to a single intravenous injection of salvarsan in a syphilitic patient. The parasites disappear more or less from the blood of the former, just as the spirochetes do from the lesions of the latter. If, then, one sees his patient at, say 8 a. m., parasites will be present, and quinin should be given. If he does not see him until noon, the parasites, with their containing cells, will have been destroyed. Therefore, quinin should not be given. The rule is, itself, *prima facie* evidence that its author believed quinin capable, under certain conditions, of inducing hemoglobinuria, yet the administration of the drug is made to depend on whether the physician sees his patient one hour or four hours after the hemoglobinuric condition has developed.

The truth is that this teaching was a groping, tentative half-step in the right direction in the right direction because it prescribed what not to do in about one-half the cases. In the light of present-day knowledge it is irrational. In the light of the actual recorded experience of physicians the world over it is a dangerous teaching and it should disappear utterly from the text-books of medicine.

The foregoing applies, of course, to the treatment of blackwater fever during the period of hemoglobinuria. When this has cleared up, when hemoglobin casts are no longer to be found and when the icterus has more or less disappeared, the question of treating the malaria — which question was solved temporarily by the destruction of a great many of the parasite-containing corpuscles — will have to be met. (It was met in one of my wards since this paper was written by the intramuscular injection of  $7\frac{1}{2}$  grains of quinin. In two hours the hemoglobinuria reappeared and that night the patient died.) Quinin will have to be given, but there need be no hurry about beginning it. If parasites reappear in the blood, they will be scant. Usually their presence will be attended by little or

no constitutional disturbance, even during sporulation, provided the patient be kept at rest. There may be a chill and fever, but, as a rule, the fever, even though the parasites be of the estivo-autumnal type, will be intermittent or markedly remittent. It is not dangerous. The danger lies in the more or less unavoidable resumption of the quinin which precipitated the paroxysm of hemoglobinuria. Neither parasites in the blood, nor chill and fever, with or without parasites, indicate quinin until the urine has been clear for several days. Of course, the blood should be examined daily, in the exceedingly remote event that a heavy infection might reveal itself. It is our practice here to begin with one-grain doses of quinin tannate three times a day and gradually to work up to 20 or 30 grains of the hydrochlorid daily. The tannate is chosen, not because it is a tannate, but because it is the weakest of the salts of quinin.

From the foregoing one may see that I have the following working conception of blackwater fever. It is, as Stephens says, a condition, not a disease, a condition incident to an heroic effort of Nature to rid the organism of the products of long-continued, and, perhaps, "exalted," malarial infection.

#### GENERAL TREATMENT

The general treatment of the condition is nearly as important as the abstinence from quinin. The chief indications are two—to supply water abundantly and to nurse carefully. On account of the distressing vomiting, it is usually necessary to supply the water as normal saline solution by bowel, by hypodermoclysis, or intravenously, according to the urgency of the case. As a rule, the "Murphy drip," given continuously, at the rate of 75 drops to the minute, is quite satisfactory. The vomiting and hiccough are frequently distressing symptoms difficult to meet. For the vomiting the best treatment is to refrain from putting anything whatever into the stomach and to put a mustard plaster over it. If these fail, it is well to make the patient drink a glass of water, into which two or three drams of bicarbonate of soda are dissolved. After this is vomited more or less relief frequently ensues. Should these simple measures prove unavailing, the changes may have to be rung on the usual remedies and the usual morphin finally resorted to. It is, however, distinctly harmful and we should turn to it only in despair.

Digitalis and caffeine, both given intramuscularly and in full doses, are of decided value in the progressive heart weakness, and as promoters of renal activity. Yorke's<sup>15</sup> studies on the mechanism of the suppression of urine in blackwater fever have shown very clearly the importance of sustaining a relatively high blood-pressure by means of fluids and of these drugs.

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15 Yorke, Warrington. Brit Med Jour., 1911, ii, 1272

Careful intelligent nursing that saves every particle of the patient's strength is of immeasurable value. A blackwater patient is emphatically a bed patient. He should be carefully watched not only during the period of hemoglobinuria, but for many days thereafter. Sudden death, by acute cardiac dilatation, during convalescence as a sequence of getting out of bed, occurred in three of our cases <sup>16</sup>

#### QUININ PROPHYLAXIS AND BLACKWATER FEVER

Whoever has read thus far has probably been struck by two things (1) the remarkably high incidence of, in Deaderick's phrase, the "mystic syndrome" among our employees, and (2) the large size of the prophylactic doses of quinin that we urge on them.

The principle of the prophylaxis of malaria by means of quinin does not, I think, need discussion. Without this measure, the present successful attempt to build the Madena-Mamorie Railroad would have ended in failure, as did the three previous attempts. I have been in the habit of urging all employees, not protected by screened houses, to take 10 grains of quinin daily, for the simple reason that smaller doses have, by actual trial, in the persons of thousands of men, been found to be far less efficient. Unfortunately, our organization is a civil, not a military one. We cannot compel our people to take quinin except when they are in the hospital. We must rely on moral suasion. The result is that some of our employees take 10 grains of quinin daily, a larger number of them take it irregularly, and a not inconsiderable number of them take absolutely no quinin, except when they are sick in bed. Now, we know, by careful observation extending over five years, that among our regular takers of quinin, blackwater fever is exceedingly rare. It does occur among them sometimes, but in these individuals there is always the history of many mild attacks of malaria, extending over many months, in spite of the daily quinin. Of those who take a good deal of quinin irregularly, and among whom the incidence of the condition is very high — 4 per cent of all admissions for all causes — the Spanish laborer is preeminent. I have already touched on this man's habits. In the first place he will not begin prophylactic doses of quinin until after malarial infection has already revealed itself in the form of a series of blood-destroying paroxysms. This, I may here say, is the serious drawback to the prophylaxis of malaria by means of quinin, it takes a good stiff attack to teach the average man — American foreman as well as Spanish peasant — that, except in our towns where antimosquito work has been done, he must take quinin daily in order to live and work here. After two or three sporulations have occurred the mischief has been done, and the only way to keep your man from becoming a subject of chronic

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<sup>16</sup> The many interesting questions connected with post-hemoglobinuric fever are deferred for future consideration.

malaria and, therefore, a candidate for blackwater fever, is to put him in the hospital and give him 30 grains of quinin every day for two or three weeks. To return to our Spaniard after having had a few attacks of malaria he begins taking quinin irregularly and resumes the pick and shovel. Malarial paroxysms recur every one or two weeks. As he uses the mosquito net, which we have forced on him, as a pillow instead of as a protection against mosquitoes, he is constantly being reinfected. Every attack saps more and more of his vitality. Finally comes the state described by Stephens, that "condition in which quinin, other drugs, cold, or even exertion, may produce a sudden destruction of red cells." In my cases, however, the exciting cause has always been quinin.

Among those of white blood who take quinin only when they are compelled to do so, blackwater fever is common. The condition developed in one of our patients — a Christian Scientist — after a single dose of 5 grains of quinin had been taken. The man had, in camp, two previous definite and separate attacks of chill and fever. On the third attack, at the entreaties of his friends, his religious scruples weakened, and he took 5 grains of quinin. In a few hours hemoglobinuria supervened and the next day he died. This 5-grain capsule of quinin was the only quinin the man had ever taken in his whole life. I do not know absolutely that the two previous definite attacks of chill and fever were malarial, but, if they were not, then this man was the only one of the party of engineers who escaped malaria during that period. No autopsy was held.

Blackwater fever is increasing among our employees. Its incidence is three times as high this year as it was in the year 1909, but in 1909, when a man had had a few attacks of malaria, he usually left the region. This condition of affairs does not now obtain. We are acquiring a population of men who have been here more than one year, men who, by reason of their intensely malarial surroundings and their failure to carry out the quinin prophylaxis properly, have become "blackwater candidates."

#### SUMMARY

1 There exists a deplorable confusion as to the cause and treatment of blackwater fever.

2 So far as may be indicated by this series of 514 cases, malarial infection stands in a direct causal relation to blackwater fever.

3 Blackwater fever is not due to a particular species of malarial parasite.

4 Quinin, in large or small doses, was, in this series, an invariable antecedent of the hemoglobinuric condition.

5 Under no circumstances<sup>17</sup> should quinin be given to a blackwater fever patient during the period of hemoglobinuria, nor for several days thereafter. The effect of the paroxysm of hemoglobinuria is, itself, that of a drastic, but temporary, therapeutic agent, decimating the malarial parasites in the patient's blood much as a single intravenous injection of salvarsan decimates the spirochetes of syphilis in the lesions of that disease.

6 Quinin, cautiously begun, will be necessary, but it should not be begun until several days after the urine has become free from hemoglobin.

7 Measures which sustain the blood-pressure are urgently indicated during the period of hemoglobinuria. Of these, normal saline solution given by bowel, subcutaneously, or intravenously, is chief. Digitalis and caffeine are of decided value.

8 The prophylaxis of malaria is the prophylaxis of blackwater fever.  
Candelaria Hospital

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17 Since this paper was written I have read a report of J. B. Cardamatis. Sixty-five physicians report 1,906 cases of blackwater fever treated with quinin, with 255 deaths, a mortality of 23.6 per cent. Forty physicians report 1,066 cases treated without quinin, with 80 deaths, a mortality of only 7.5 per cent. Cardamatis, John P. Bull. Soc. de path. exotique, 1910, III, 104.

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